

STUDIES IN THE CHEMISTRY OF ENOL PHOSPHATES
AND RELATED COMPOUNDS

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degree of Doctor of Philosophy in Chemistry
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by

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CONTENTS

	Page
ABSTRACT	1
INTRODUCTION	2
Scope and Limitations of the Perkow Reaction.....	8
Mechanism of the Perkow Reaction.....	10
Other Products from α -Halogenocarbonyl Compounds...	23
EXPERIMENTAL	
Introduction.....	28
Preparation of Compounds.....	30
Reactions of α -Halogenocarbonyl Compounds with Triethyl Phosphite.....	47
RESULTS AND DISCUSSION	86
Possible Origins of Dehalogenated Products.....	87
Evidence for Ionic Mechanism of Dehalogenation.....	90
Radical Mechanism of Dehalogenation.....	96
Scope and Limitations of the Dehalogenation Reaction.....	101
The Formation of Vinyl Phosphonates.....	108
Reaction of Dichloroacetamide Derivatives.....	116
Mechanism of the Perkow Reaction.....	117
CONCLUSION	122
APPENDIX	125
REFERENCES	127

ABSTRACT

The reactions of the trichloroacetamide derivatives, Cl_3CCONHY where $\text{Y} = \text{CONH}_2, \text{CONMe}_2, \text{COCH}_2\text{Cl}, \text{CSNH}_2$ and CSNHet with triethyl phosphite have been studied. The major products of the reactions were the corresponding dichloroacetamide derivatives and these were shown to result from an ionic mechanism involving initial attack by phosphite on halogen. The reactions of other α -halogeno-carbonyl compounds with triethyl phosphite were studied in protic solvents and the relevance of the results obtained, to the mechanism of the Perkow reaction, is discussed.

In dilute solution some of the trichloroacetamide derivatives gave unexpected products which were identified as vinyl phosphonates, $(\text{EtO})_2\text{P}(\text{O})\text{C}(\text{NH}_2)=\text{CCl}_2$. A mechanism is suggested for their formation.

Similar dichloroacetamides $\text{Cl}_2\text{CHCONRY}$, were found to give vinyl phosphonates for $\text{R} = \text{H}$ and enol phosphates when $\text{R} = \text{alkyl}$. Monochloroacetamides were not observed as products in any of these reactions.

INTRODUCTION

Trialkyl phosphites are strong nucleophiles and react readily with alkyl halides to produce phosphonates.¹

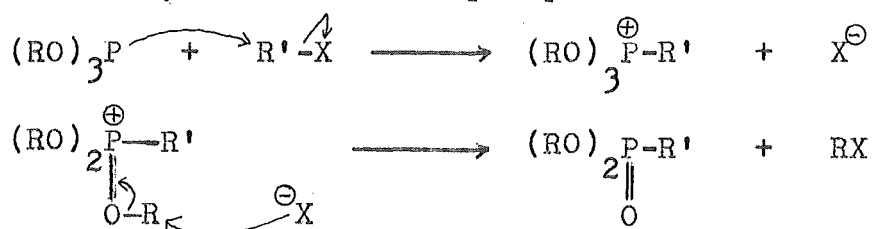


The reaction is known as the Michaelis-Arbusov or Arbusov reaction, and is a general reaction of alkyl halides with trivalent phosphorus compounds containing at least one alkoxy group.

Phosphines also react with alkyl halides but form instead a stable phosphonium salt.



Consequently, it is generally accepted that the Arbusov reaction proceeds in two stages: an initial quaternisation of the phosphite by nucleophilic attack on the halide, and then dealkylation of this phosphonium intermediate*



There is some controversy over which step is rate determining. According to Harvey and De Sombre² it is the

* Often referred to as a quasi-phosphonium intermediate.

The term "quasi" arose due to some question as to whether the intermediate was a true ionic species, an ion pair, or a pentacovalent species.

second, but their evidence is inconclusive and does not justify this assumption. More recent evidence reviewed by Marmor³ suggests that the opposite is generally the case. The most convincing of this is the quantitative evidence of Aksnes and Aksnes.⁴ They showed that, for the rearrangement of triethyl phosphite to diethyl ethylphosphonate in the presence of ethyl iodide,



- (a) the concentration of ethyl iodide remains constant throughout the course of the reaction,
 - (b) the rate of product formation is proportional to the concentration of ethyl iodide,
 - (c) the rate is not affected by added iodide ion and,
 - (d) the reaction was found to be faster in polar solvents (acetonitrile) than in less polar solvents (benzene). These results are uniquely consistent with a rate-determining first stage, i.e. formation of the phosphonium intermediate.
- (Naturally, by suitable choice of reagents it is possible to favour a slow second step. For instance, with triaryl phosphites, phosphonium intermediates have actually been isolated⁵, since the dealkylation step cannot readily take place.

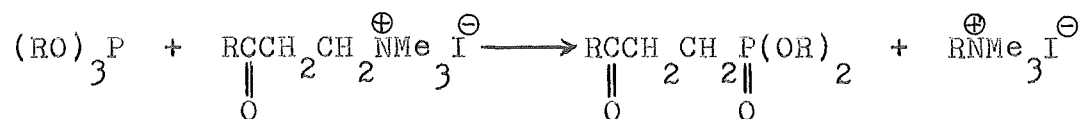


The reactivity sequence for the Arbuzov reaction, $\text{Et}_2\text{P}(\text{OEt}) > \text{EtP}(\text{OEt})_2 > \text{P}(\text{OEt})_3$ can be explained in terms of a slow first step by a dependence of the nucleophilic

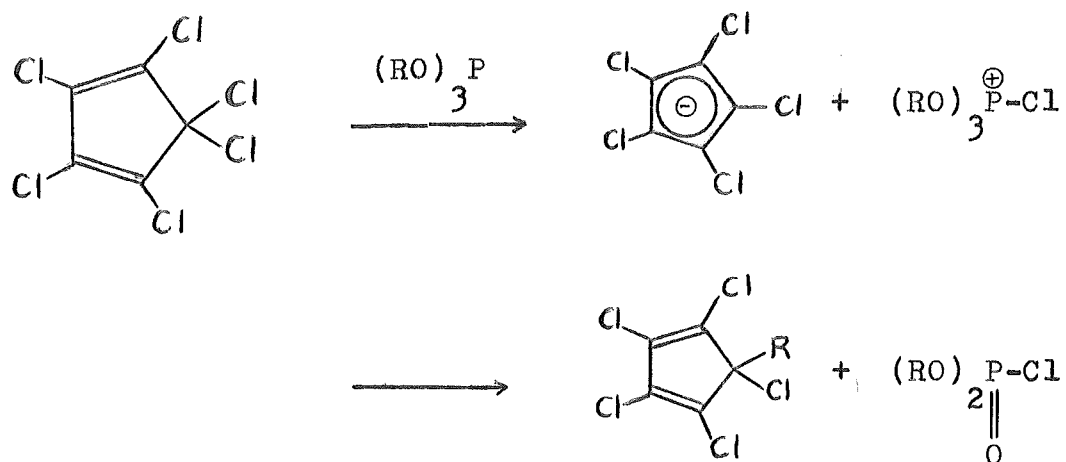
reactivity of the phosphorus on inductive effects. The halide reagent reactivity sequences, acyl > primary alkyl > secondary alkyl, and iodide > bromide > chloride, are also consistent with a slow S_N2 attack by phosphorus.

The dealkylation of the phosphonium intermediate is generally regarded as a simple bimolecular displacement at saturated carbon⁶ and many other reactions of P(III) compounds, like the Arbusov reaction, end with a final irreversible dealkylation step².

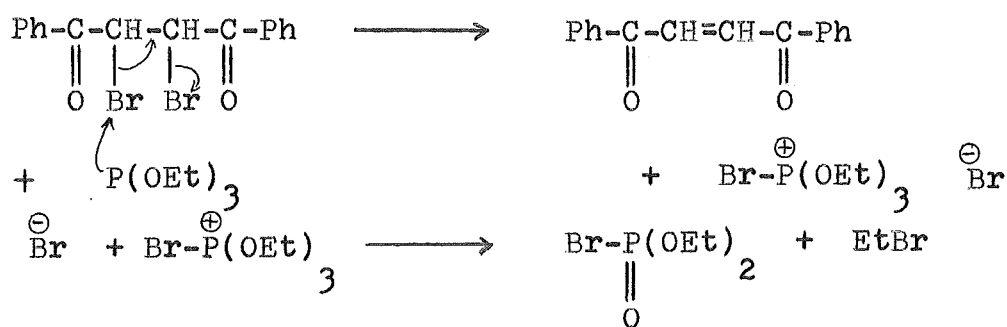
Trialkyl phosphites react in a similar way with other compounds that have a good leaving group attached to saturated carbon to give phosphonates, e.g. lactones, sulphonate esters, anhydrides, and quaternary ammonium compounds².



The reaction however is not entirely general. An alternative nucleophilic attack of phosphite on halogen rather than carbon appears to be favoured in certain cases; most notably in those where the anionic product, if formed, would be expected to have some stabilising factor. The best known examples of this attack on halogen are found in the case of perhalocyclopentadienes. These, on reaction with trialkyl phosphites convert the phosphite to phosphorochloridate and are themselves alkylated.⁷



Other examples are to be found in certain vic-dihalides. The exceptions usually occur when the dihalide is so substituted as to allow appreciable stabilisation of the carbanion which would be formed if elimination of the halide ion were not simultaneous with removal of the positive halogen, e.g.⁸



α -Halogeno carbonyl compounds often react abnormally to give enol phosphates instead of phosphonates. This is the Perkow reaction.⁹

The situation was resolved in 1952 when Perkow⁹ discovered the product of the reaction of chloral with triethyl phosphite was not a ketophosphonate but the isomeric dichlorovinyl phosphate.

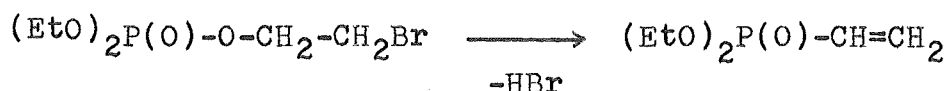


Formulation of this product as an enol phosphate rested on the following evidence;

1. It did not give any of the reactions characteristic of aldehydes that would be expected if it were the aldophosphonate, $(\text{EtO})_2\text{P}(=\text{O})-\text{CCl}-\text{CHO}$.
2. It added one mole of chlorine to give a tetrachloride.
3. Hydrolysis with concentrated hydrochloric acid gave orthophosphoric acid. Under the same conditions the P-C bond of a ketophosphonate is stable and hydrolysis would give a phosphonic acid.

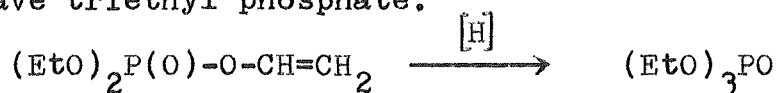
Allen and Johnson¹² confirmed this structure and showed that the Perkow reaction was a general one for many α -halogenocarbonyl compounds. Perkow's initial assignment of the compounds as enol phosphates was strongly supported by further evidence;

1. The products showed IR absorption around 1640 cm^{-1} characteristic of an olefinic double bond.
2. Diethyl vinyl phosphate was synthesised by the dehydrobromination of diethyl 2-bromoethyl phosphate



and proved to be identical to the product obtained by the reaction of chloroacetaldehyde and triethyl phosphite.

3. Hydrogenation of diethyl vinyl phosphate, obtained from the reaction of triethyl phosphite and chloroacetaldehyde, gave triethyl phosphate.

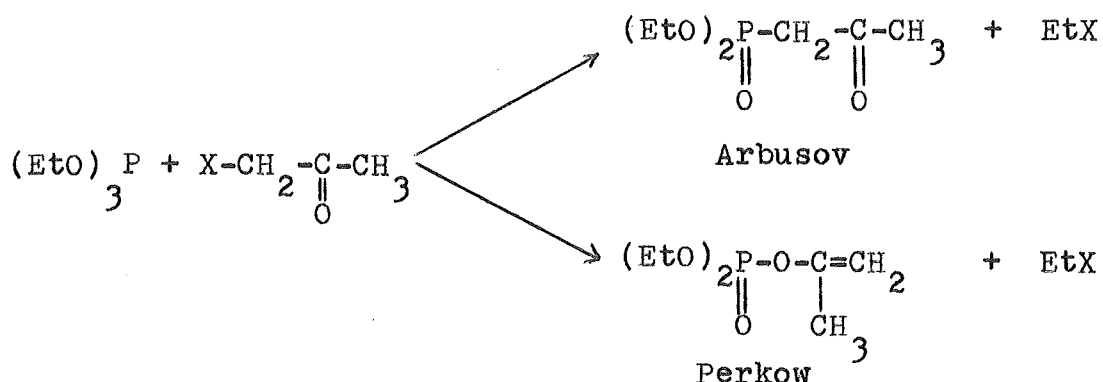


Scope and Limitations of the Perkow Reaction.¹³

- (a) In general α -haloaldehydes react with trialkyl phosphites to yield enol phosphates exclusively. e.g.



- (b) With α -haloketones a mixture of Perkow and Arbusov products frequently results. The proportions of each present have been shown to depend on a number of factors such as temperature, solvent, and the nature of halogeno-group. e.g. for the monohaloacetones¹⁴



RATIO OF ENOL PHOSPHATE TO PHOSPHONATE PRODUCED

	At <u>ca.</u> 150°	In refluxing ether
$\text{ClCH}_2\text{COCH}_3$	90:10	---
$\text{BrCH}_2\text{COCH}_3$	20:80	80:20
$\text{ICH}_2\text{COCH}_3$	---	10:90

Thus the Perkow reaction is favoured over the Arbusov by low temperatures and by the use of chloro compounds rather than bromo- or iodo- ones.

It has further been shown that any substituents on the α -carbon, and in particular those which are strongly electron-withdrawing e.g. carbonyl or halogen, favours the Perkow reaction.

(c) α -Haloesters are generally unreactive and it is only the activated esters such as trichloroacetates and halomalonates that give enol phosphates.



Monohaloesters react solely at the α -carbon to give Arbusov products, as do monohaloamides,



while the dihaloesters give many products boiling over a range of temperature, none of which have been identified.

(d) Trichloroacetamides do not give either phosphonates or enol phosphates but give instead trichlorovinylamines

and trialkyl phosphates.¹⁵



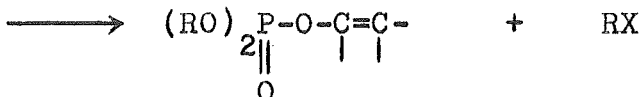
(R = alkyl, aryl)

It would appear that, in general, the effect of structure of the halogenocarbonyl compound on the partition of the reaction between Perkow and Arbusov products, is what one would expect to arise as a result of competition between the α -carbon and carbonyl carbon as sites for nucleophilic attack by phosphite, but as will become apparent in the next section, the position is by no means as simple as this.

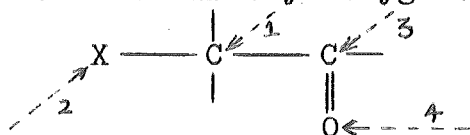
Mechanism of the Perkow Reaction.-

There is at present no universally accepted mechanism for the Perkow reaction. A number have been proposed, each supported to some extent by experimental evidence, but in no case has it been possible to rule out all others. It is likely that more than one may operate.

All of the favoured mechanisms have one common feature - they all propose attack of the trialkyl phosphite as a nucleophile on the α -halogenocarbonyl compound, leading eventually to the formation of an enol phosphonium intermediate, which is subsequently dealkylated by attack of halide ion to give the enol phosphate.



Their major point of divergence is the site of initial attack. Nucleophilic attack is favoured at two sites on the molecule - carbonyl carbon and α -carbon - and nucleophilic attack by phosphorus is also possible at halogen and even at carbonyl oxygen.



The final irreversible dealkylation of the enol phosphonium intermediate, common to all four mechanisms, is generally considered to be a fast process as in the Arbuzov reaction. (There is no direct evidence on this point for the Perkow reaction, but since the rate can vary widely for the reaction of a given phosphite with different carbonyl compounds it is unlikely that the common dealkylation of very similar enol phosphonium cations can be rate-limiting). Consequently the problem of mechanism rests on the identification of the point at which initial attack takes place. The various alternatives suggested above will now be considered separately in detail.

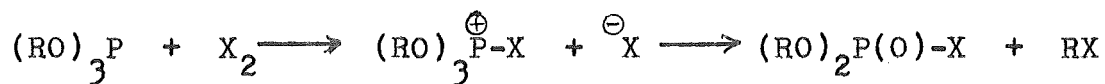
perchlorates in benzene, proved to be stable and showed no tendency to rearrange.¹⁷

It has also been shown¹⁸ that the introduction of electron-withdrawing groups into the aromatic ring of ω -bromoacetophenones increases the proportion of enol phosphate formed at the expense of the phosphonate when they are reacted with triethyl phosphite. This effect is best explained by different reaction paths for the two products.

Thus initial attack at the α -carbon can be ruled out.

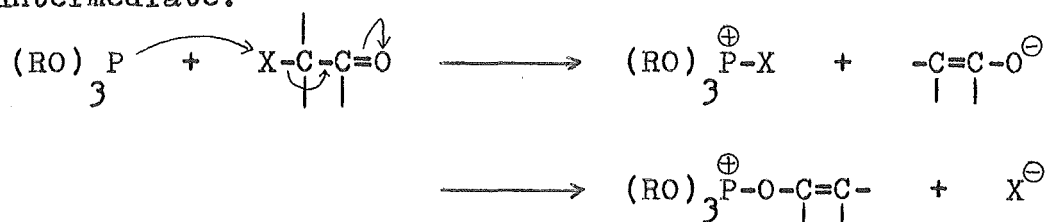
Attack on halogen

Many reactions are known where there is nucleophilic attack by phosphite on halogen,¹⁹ the simplest of these being the preparation of phosphorohalidates from halogens.

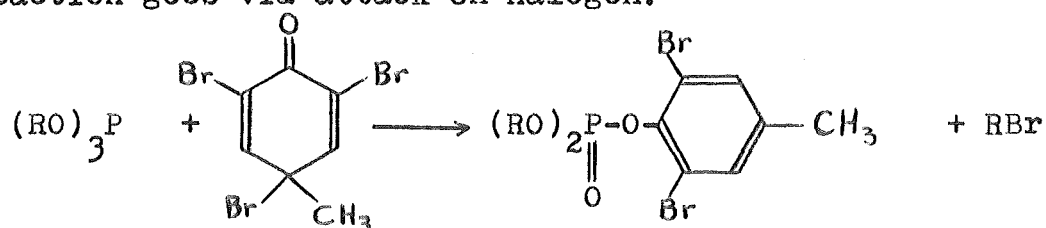


Other examples include such obvious sources of positive halogen as tert. alkyl hypochlorites, and polyhaloalkanes (e.g. ClF_3). Compounds where removal of halogen as X^+ leaves a resonance stabilised anion (see P. 5), are also susceptible to attack at halogen by phosphites. These include the α -halogenocarbonyl compounds since the anion produced by abstraction of X^+ is an enolate anion, which is stabilised by resonance. This displaced anion could then react with the chlorophosphonium cation, bond formation occurring with the oxygen, to give the enol

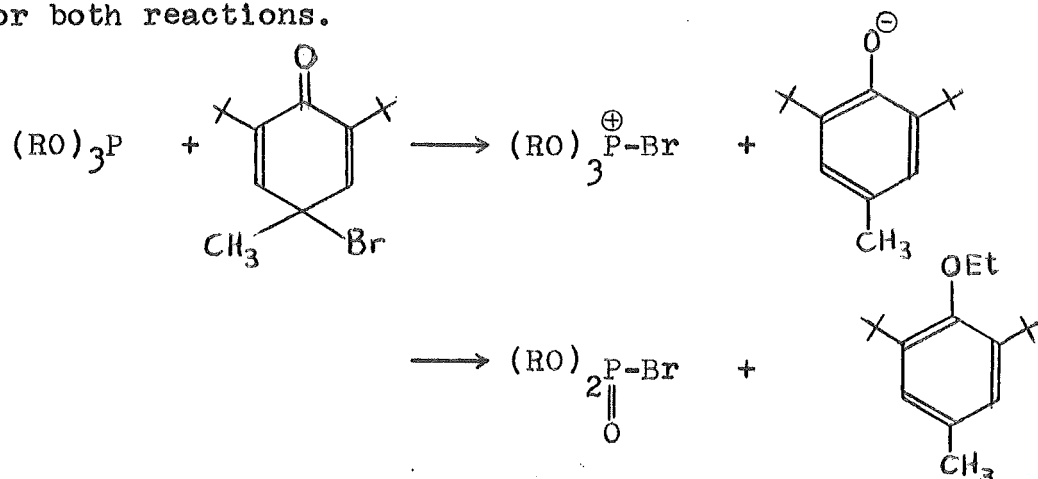
intermediate.



Miller has shown that 4-bromocyclohexadienones react with trialkyl phosphites to give aryl dialkyl phosphates²⁰ and put forward evidence that this reaction goes via attack on halogen.



When the two ortho bromine atoms are replaced by tert. butyl groups, O-alkylation rather than phosphorylation occurs without any significant decrease in rate of reaction, suggesting the initial attack is on bromine for both reactions.

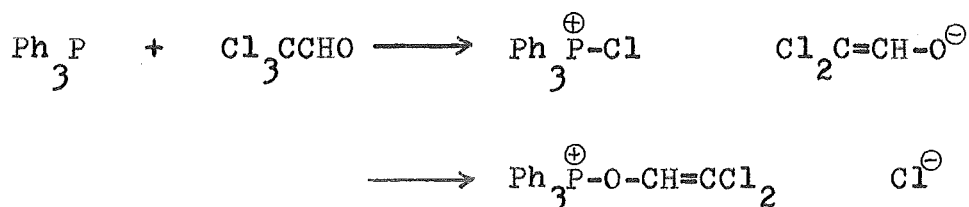


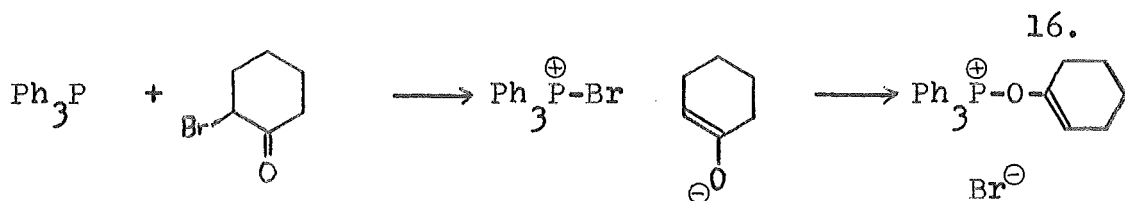
The aryl phosphate obtained from the tribromocyclohexadiene-^{1,3}one is analogous to an enol phosphate and Miller suggested this as supporting evidence for attack at halogen for the Perkow reaction.

In the case of α -halogenocarbonyl compounds, attack

at halogen as the initial step in the Perkow reaction has been postulated mainly on evidence obtained from reactions of phosphines. It was first suggested by Speziale and Smith²¹ who found that dichlorofluoroacetamides react more slowly with phosphines than do trichloroacetamides. They explained this by proposing attack at halogen to give a carbanion which would be stabilized less by a fluorine atom than by a chlorine atom. Furthermore, if attack at the carbonyl oxygen or carbonyl carbon occurred, then an increase in reactivity would be expected because of the greater inductive effect of fluorine. Also, the reaction of α,α -dichloro- α -phenylacetamides with triphenylphosphine has been shown to be a 2nd order polar reaction which is strongly accelerated by electron withdrawing substituents in the α -phenyl group²² ($\rho = +2.6$). Such results are consistent with a mechanism involving initial attack on chlorine.

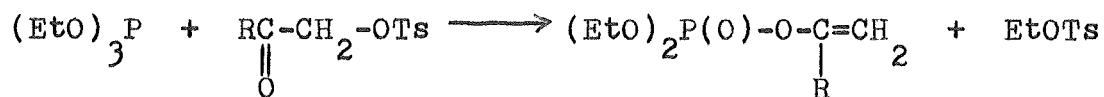
Other α -halogenocarbonyl compounds react with phosphines to give enol phosphonium compounds and the evidence suggests these also proceed by initial attack on halogen²³.





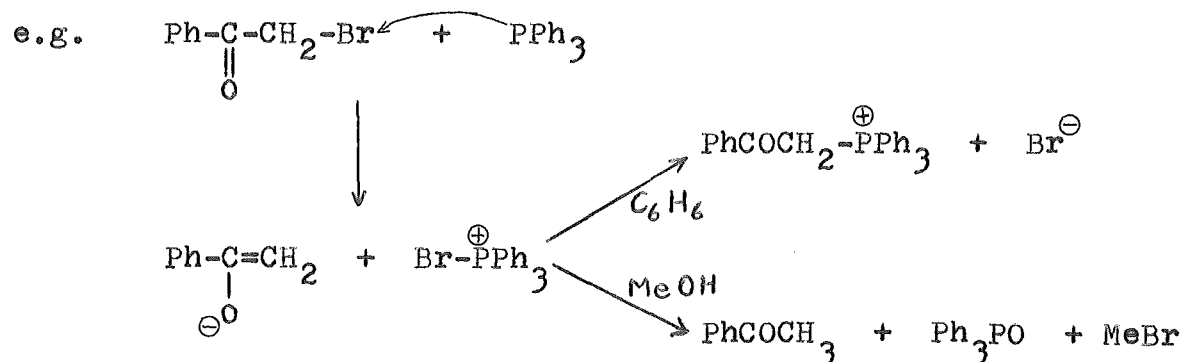
It has generally been assumed that the reaction of phosphites to give enol phosphates proceeds by a similar mechanism. However, this assumption is probably not justified. For instance; Hudson²⁴ has observed that whereas α -bromocyclohexanone reacts rapidly with triphenylphosphine at 0°, α -chlorocyclohexanone does not react on boiling in benzene for 48 hours. Steric hindrance prevents S_N2 displacement on these compounds and the difference in reactivity is in agreement with the proposal^{23c} that triphenylphosphine reacts at the bromine. Yet α -chloro- and α -bromocyclohexanone both react at similar rates with trialkyl phosphites to give enol phosphates.^{17,18} It appears therefore that phosphines and phosphites do not necessarily attack the same electrophilic centre.

Evidence against halogen attack has come from an investigation of the reaction of α -keto-p-toluenesulphonates with triethyl phosphite and triphenylphosphine.²⁵

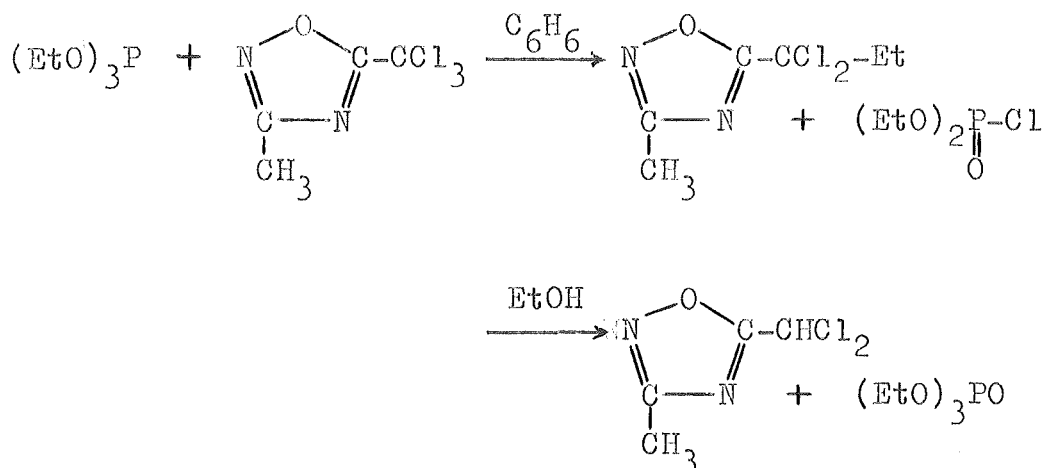


The ready formation of enol phosphate here, where there is no halogen to attack, suggests that the halogen is normally displaced as an anion. Since the triphenylphosphine attacks the α -carbon and such attack has been ruled out for the Perkow (see previous section) this is once again evidence that phosphines and phosphites may attack different sites of the molecule. Enol phosphates are also formed from α -keto-sulphides and -alcohols.²⁶

Protonation of enolate anions produced by attack at halogen has been shown to lead to reductive dehalogenation in the reactions of both phosphines²⁷ and phosphites²⁸.



(The C-phosponium salt formed in this reaction of ω -bromoacetophenone with triphenylphosphine in benzene was shown to be stable to methanol. Yet, when the reaction was carried out with methanol as solvent, acetophenone was formed, indicating that the phosphine is attacking bromine and the resulting enolate anion is being trapped by methanol).



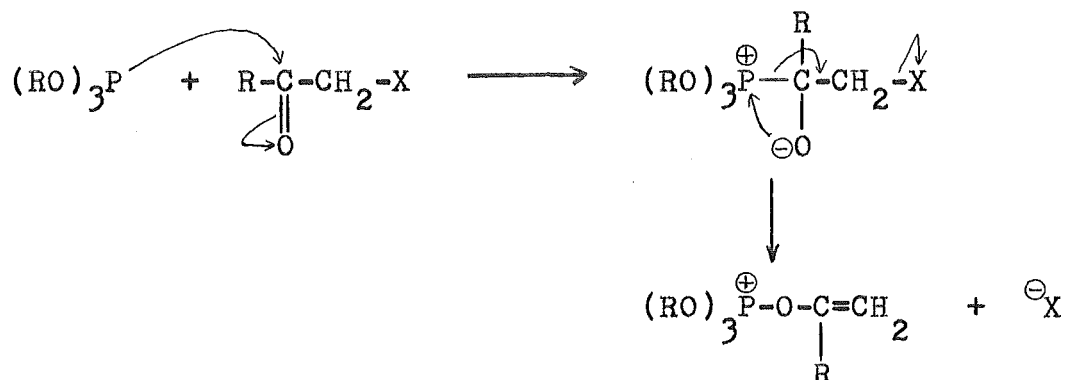
On the other hand high yields of enol phosphates can still be obtained from both α -chloro-, and α -bromoketones in protolytic solvents.^{17,18} This must be considered to rule out halogen attack as a path for enol phosphate formation in these cases.

It appears therefore that, although attack on halogen seems to occur in the reactions of triphenylphosphine, it is unlikely to be the initial step in the Perkow reaction.

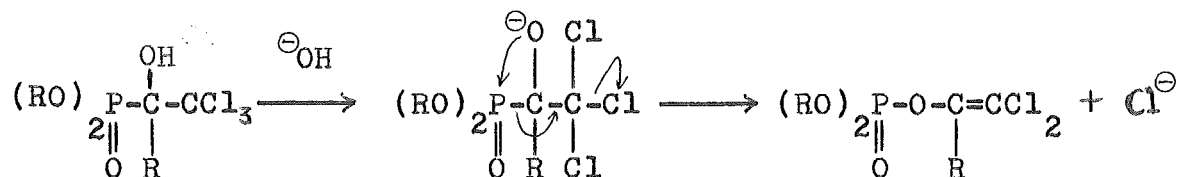
Attack at the carbonyl carbon.

The carbonyl carbon is the most electrophilic centre in the molecule and a number of authors have suggested initial attack at this position.^{17,18,29,30} Dialkyl phosphites and their anions react here to give α -hydroxy-phosphonates and epoxy-phosphonates respectively³¹ and by analogy, the mechanism of the Perkow, as originally proposed by Allen and Johnson¹², can be explained by initial addition to the carbonyl group, followed by a three-centre rearrangement of the

phosphonium alkoxide produced.

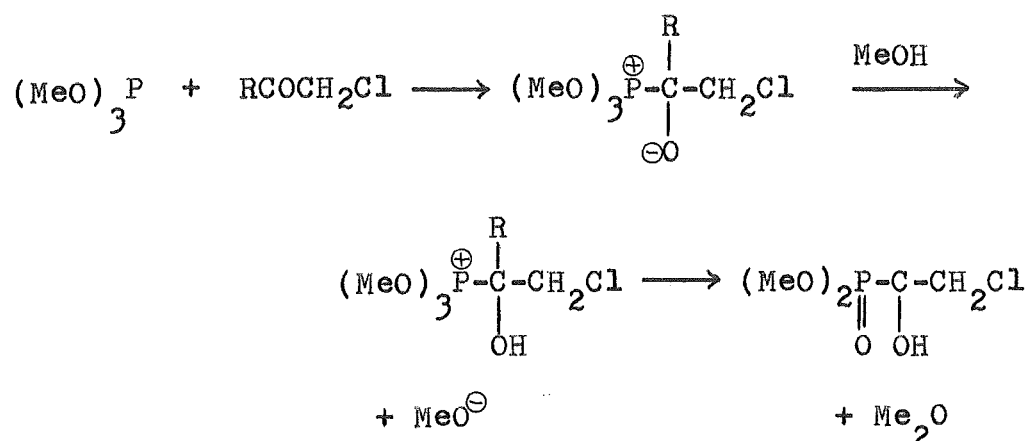


Similar rearrangements of 1-hydroxyphosphonates are known to proceed rapidly.²⁹ These are base catalysed and removal of a proton from the hydroxy group gives an alkoxide ion which might be expected to react in a similar way to the phosphonium alkoxide above.

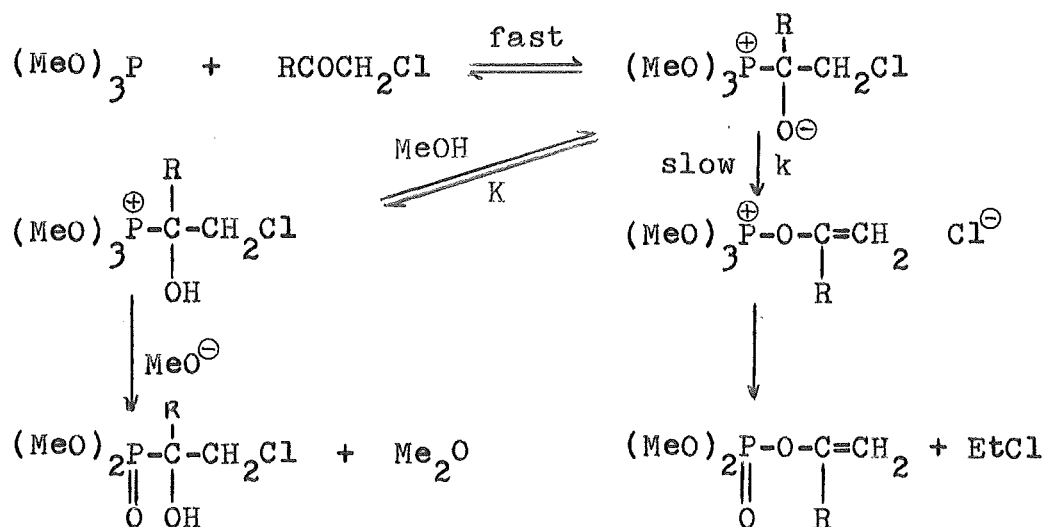


The phosphonium intermediate, however, would be expected to rearrange much faster because of the greater electrophilicity of its P^+ centre, and hence successfully compete with the final dealkylation stage of the reaction.

Evidence for the intermediate phosphonium adduct is provided by the isolation of 1-hydroxyphosphonates from the reaction of trimethyl phosphite with chloroacetone or phenacyl chloride in methanol.¹⁷ Small amounts (15-30%) of enol phosphate are also formed suggesting that the rearrangement and protonation followed by dealkylation, are competing reactions.



Rearrangement is favoured in ethanol which is a weaker acid than methanol. In the case of bromoketones, rearrangement accompanied by elimination of bromide ion might be expected to occur more readily than for chloroketones. Good yields of enol phosphates are indeed formed in methanol under these conditions. In acetic acid even bromoketones give considerable amounts of hydroxyphosphonate. Kirby and Warren³² suggest that the mechanism requires a rapid reversible addition of the phosphite, followed by a slow rate determining rearrangement step, to explain these effects.



The yield of 1-hydroxyphosphonate is increased by an increase in K (MeOH to AcOH) or a decrease in k (chloroacetone < bromoacetone).

These facts leave little doubt that the phosphonium intermediate is present in solution under the conditions where the Perkow reaction occurs and Chopard et.al.¹⁷ claim that initial attack at carbonyl carbon is a highly likely mechanism for the Perkow reaction. However, they also note that an alternative path involving initial attack carbonyl oxygen cannot be eliminated since addition at carbon is reversible and may not actually lie on the pathway to enol phosphate formation.

Attack on carbonyl oxygen.

Direct nucleophilic * attack on oxygen has the advantage of being the simplest mechanism in that the enol phosphonium intermediate is formed directly.

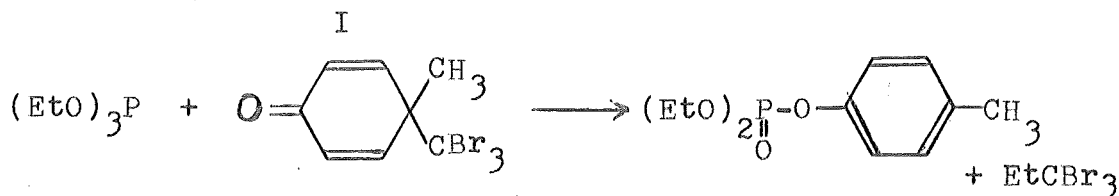


Several authors³³ have suggested it but there has been no convincing evidence to support it. As this same

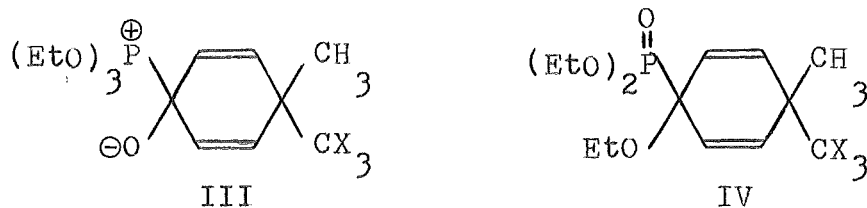
* Electrophilic attack by phosphorus on oxygen has also been considered by Hudson¹⁷ but discarded as an improbable mechanism on the grounds that it is inconsistent with the sequence for reactivity of the carbonyl compounds, i.e. substituents which increase the electrophilic character of the carbonyl carbon also increase reactivity.

intermediate must be formed in any mechanism for the Perkow reaction it will be difficult to accumulate evidence either for or against it. However, it is well known that trivalent phosphorus does attack electronegative centres and in particular, trialkyl phosphites are thought to attack the carbonyl oxygen of compounds such as quinones, 1,2-diketones³⁴ and others which are capable of stabilising a negative charge at the carbonyl carbon, e.g. $\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CHO}$ ³⁵.

One case where direct evidence has been obtained for such an attack comes from vinylogous reactions of 4-trihalo-4-methylcyclohexa-2,5-dienones.³⁶ Reaction of triethyl phosphite with the 4-tribromo compound I gives the aryl phosphate,



whereas the corresponding 4-trichloro compound II gave no reaction. If attack at carbonyl carbon were the rate determining step then one would expect II to be more reactive because of the greater inductive effect of the CCl_3 group. If it were the fast step then the rearrangement of the adduct III would be slow and hence yield some of the 1,1 substituted cyclohexadiene IV.



This was not found, so the reaction must be assumed to take place by attack at carbonyl oxygen.

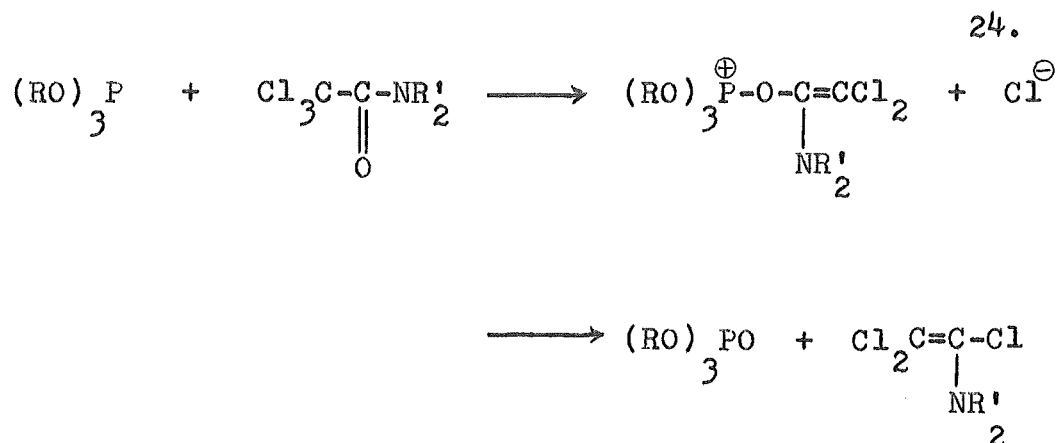
Chloro- and bromocyclohexanone react at about the same rate in competition for triethyl phosphite. In the case of isobutyrophenones, the chloro- reacts faster than the bromo-derivative.¹⁸ This observation is difficult to explain by the S_N2' mechanism involving initial attack at oxygen. However for most compounds it is generally assumed that the reactivity sequence $I > Br > Cl$ holds.

Apart from this discrepancy, attack on carbonyl carbon and carbonyl oxygen explain the observed facts equally well and it is not possible to decide between them. Both appear likely for monohalogeno-carbonyl compounds, but for trihalo - compounds where there is more steric hindrance to the carbon, and the Perkow reactions still proceed vigorously, the oxygen is considered to be the site of attack, e.g. Cl_3CCONR_2 ¹⁵, and tribromomethyl 2,4,6-trimethylphenyl ketone.³⁷

Other Products from α -Halogenocarbonyl Compounds.-

Vinylamines.

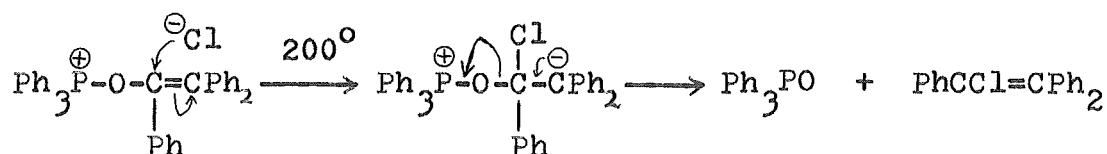
Earlier (P. 9) it was mentioned that N,N-dialkyl-trichloroacetamides do not give enol phosphates with trialkyl phosphites but react to form trichloro-vinylamines. These products are believed to form as a result of breakdown of the enol phosphonium intermediate.¹⁵



Phosphines react similarly to give vinylamines and phosphine oxides. ^{15,21}

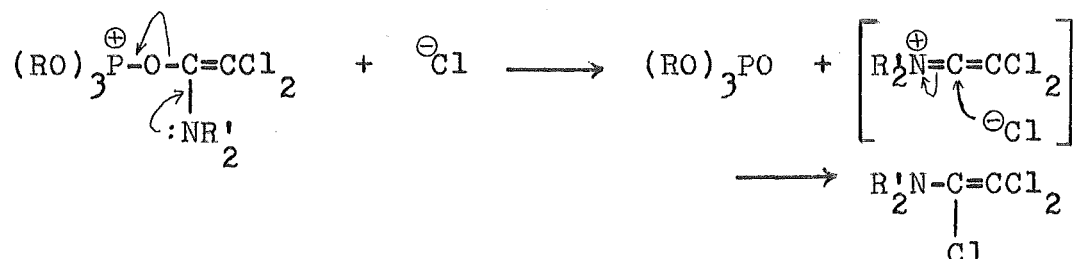


The displacement of triphenylphosphine oxide from the phosphonium salt derived from chlorodiphenylacetophenone and triphenylphosphine proceeds only under vigorous conditions. The product of this breakdown is chlorotriphenylethylene and it is thought to form by an addition-elimination mechanism.³⁸

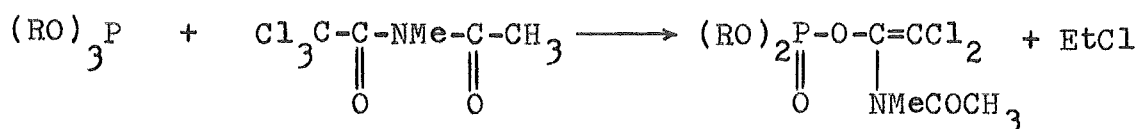


From the observation that this type of halo olefin is formed readily from trichloroacetamides and phosphines, and even in preference to enol phosphate formation in the case of phosphites, it is apparent that an electron-donating group such as -NH_2 adjacent to the carbonyl group must facilitate the collapse of the intermediate enol phosphonium salt. The mechanism suggested by Speziale

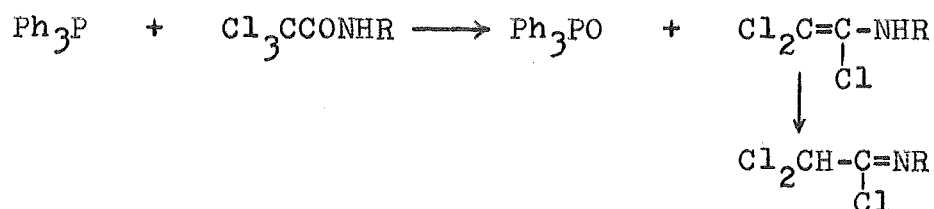
involves fragmentation prior to chloride ion attack.^{21,38}



Elimination of the stable trialkyl phosphate moiety could be the driving force for the reaction but it is undoubtedly assisted by the lone pair of electrons on the nitrogen atom. If these are not available, for example, when a second carbonyl or a sulphonyl group is attached to the amide nitrogen, fragmentation no longer occurs and enol phosphates are obtained by a normal Perkow reaction.³⁹ e.g.



When trichloroacetamides bearing at least one hydrogen on the nitrogen atom are used, imidoyl chlorides are obtained instead of the tautomeric vinylamines.²¹



Dehalogenated Products.

Many halogenated β -diketones react with trialkyl phosphites to give enol phosphates.⁴⁰ However in special cases reductive dehalogenation has been observed. Thus $(\text{PhCO})_2\text{CHCl}$, $(\text{PhCO})_3\text{CCl}$;⁴¹ $(\text{PhCO})_2\text{CHBr}$, $(\text{PhCO})_3\text{CBr}$, $\text{o-C}_6\text{H}_4(\text{CO})_2\text{CBrCO}_2\text{Et}$, $\text{o-C}_6\text{H}_4(\text{CO})_2\text{CHBr}$;⁴² $\text{Br}_2\text{C}(\text{SO}_2\text{Et})_2$, $\text{BrCMe}(\text{SO}_2\text{Et})_2$, and $\text{Cl}_2\text{C}(\text{SO}_2\text{Et})_2$ ⁴³ on treatment with trialkyl phosphite all gave their respective dehalogenated starting materials, i.e. $(\text{PhCO})_2\text{CH}_2$, $(\text{PhCO})_3\text{CH}$, $(\text{PhCO})_2\text{CHBr}$, $(\text{PhCO})_3\text{CBr}$, $\text{o-C}_6\text{H}_4(\text{CO})_2\text{CH}_2$, $\text{o-C}_6\text{H}_4(\text{CO})_2\text{CH}_2$, $\text{CH}_2(\text{SO}_2\text{Et})_2$, $\text{CHMe}(\text{SO}_2\text{Et})$, and $\text{CH}_2(\text{SO}_2\text{Et})_2$. The authors postulate that free radical intermediates may be involved. It has also been suggested⁴⁴ that the observed products might result either from hydrolysis, by moisture present, of the Perkow enol phosphonium intermediate, e.g.

$$(\text{RO})_3\text{P}^{\oplus}\text{-O-C(Ph)=CHCOPh}^{\ominus}\text{Br} \xrightarrow{\text{H}_2\text{O}} (\text{RO})_3\text{PO} + (\text{PhCO})_2\text{CH}_2 + \text{HBr}$$

or from the protanation of any enolate anion formed as a result of phosphite attack on halogen (which might be expected to occur in cases such as these where extremely stable anions would be involved). Although such an hypothesis is consistent with the structural features of the halides no evidence has been produced to substantiate it.

The reactions of trichloroacetamides with trialkyl phosphite have been studied in detail and found to give

either vinylamines, imidoyl chlorides, or enol phosphates depending on the number and type of substituents on the amide nitrogen. Since comparatively little attention has been paid to the reactions of trichloroacetamides of the type CCl_3CONHY where Y is an electron-withdrawing group, the initial aim of this work was to investigate the reactions of such compounds with trialkyl phosphites and, if possible, furnish some evidence for one of the mechanistic paths to enol phosphate formation in these cases.

However, preliminary investigations revealed that these reactions bore little resemblance to those of the other trichloroacetamide derivatives. The major products obtained were the corresponding dichloroacetamide compounds. The mechanism of this dehalogenation reaction was considered to be of interest so the system was subjected to a closer investigation.

EXPERIMENTALIntroduction.-

All melting points are uncorrected. Infra-red spectra were recorded as liquid films, unless otherwise stated, on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were recorded using carbon tetrachloride or deuteriochloroform solutions on a Varian Model A-60 spectrometer, with TMS as an internal standard. Mass spectra were recorded on an A.E.I. Model M.S.9. GIC analyses were carried out on either an Aerograph H1-Fi Model 1200, or an Aerograph Model 204 gas chromatograph using a 5' column packed with 5% SE-30 on chromosorb W.

Light petroleum refers to the fraction of b.p. 50-70°. All solvents for column chromatography and reactions were purified technical grade. Benzene and light petroleum were distilled off phosphorus pentoxide; ether and all chlorinated solvents were dried over calcium chloride. The silica gel used for column chromatography was Crosfield quality grade B.S.S. Sorbsil. The monochloro-, dichloro-, and trichloroacetyl chlorides used were commercial products while the dichloro- and trichloroacetic anhydrides were prepared by distilling the corresponding acid off phosphorus pentoxide⁴⁵. The triethyl phosphite was a commercial product and was fractionally distilled before use.

Most reactions were studied first on TLC, to determine conditions for reaction, and to help with the isolation of products. BDH "Silica Gel for TLC" was used throughout.

This was mixed with 5% fluorescein powder before use so that many of the compounds, especially vinyl derivatives, could be visualised under UV light. Chloroform-acetone mixtures were used for developing the chromatograms.

Other methods of visualisation included the use of reagents such as iodine (general), Grote's reagent for thioureas,⁴⁶ and chlorine atmosphere/potassium iodide-starch.⁴⁷ This latter method was useful for compounds with a primary or secondary amide group.

Preparation of Compounds.-Acylated Ureas.

These, with two exceptions, were prepared from the appropriate urea and acyl halide.

(a) Monochloroacetylurea

Monochloroacetylurea was prepared by the addition of chloroacetyl chloride to urea as described by Pearl and Dehr.⁴⁸ One recrystallisation from alcohol gave the product in 55% yield, m.p. 186-188°. (Lit.⁴⁸ 190-191°).

(b) Dichloroacetylurea

Dichloroacetyl chloride (24 g, 0.17 mole) was added to urea (10 g, 0.17 mole) and the mixture heated on a steam bath for one hour. After the addition of excess cold water (200 ml), the crude product was filtered off and recrystallised from ethanol, giving 11 g (38%) of dichloroacetylurea, m.p. 152-154°. (Lit.⁴⁸ 149-150°).

(c) Trichloroacetylurea

Trichloroacetylurea was prepared in 30% yield m.p. 151-152°, from urea and trichloroacetyl chloride by the method given for dichloroacetylurea. (Lit.⁴⁸ m.p. 150°).

(d) N,N'-Dimethyl-N-trichloroacetylurea

Trichloroacetyl chloride (42 g, 0.23 mole) was added to a stirred mixture of N,N'-dimethylurea (20 g,

0.23 mole) in trichloroethylene (100 ml) over a period of fifteen minutes. After refluxing for three hours, the solvent was removed under reduced pressure. The reaction mixture was added to ether (100 ml), washed with water, and dried over anhydrous magnesium sulphate. The ether was distilled off under vacuum, leaving a viscous oil which was distilled carefully through a 10 cm Vigreux column at a pressure of 0.1 mm. An impurity, N-methyl-trichloroacetamide distilled first and solidified in the condenser. Once this had been removed from the system N,N'-dimethyl-N-trichloroacetylurea was collected, b.p. 80° (0.1 mm). This crystallised on standing for a few days, and after recrystallisation from ether-light petroleum (1:1) gave 25 g (50%) of the pure compound, m.p. 42-43°. (Lit.^{39a} 34-38°).

(e) N-Dichloroacetyl-N,N'-dimethylurea

N-Dichloroacetyl-N,N'-dimethylurea was prepared by reacting dichloroacetyl chloride with N,N'-dimethylurea for two hours in refluxing benzene. After washing the reaction mixture with water and drying over anhydrous magnesium sulphate, it was distilled to give a 77% yield of compound collected at 118-120° (0.5 mm). This clear viscous oil failed to give satisfactory analyses. Attempts made to purify the product by fractionation led to decomposition. NMR (CCl₄): δ 8.53 (1 proton, singlet, N'-H), 6.43 (1 proton, singlet, CHCl₂), 3.42 (3 protons, singlet, N-CH₃), 2.88 ppm

(3 protons, doublet, $J = 5$ cps, $N'-CH_3$).

(f) N,N-Dimethyl-N'-trichloroacetylurea

Attempts to make this by direct acylation of N,N-dimethylurea failed unless triethylamine was present. (In the absence of base, two other products were obtained in good yield; N,N-dimethyltrichloroacetamide and 1,1-dimethyl-5-trichloroacetylbiuret).

N,N-Dimethylurea⁴⁹ (8.8 g, 0.1 mole) was dissolved in benzene (70 ml) containing triethylamine (15 ml, 0.11 mole). Trichloroacetyl chloride (18.2 g, 0.1 mole) in benzene (20 ml) was added dropwise over twenty minutes with stirring and the stirring was continued for a further four hours at room temperature. After cooling the mixture in ice, it was filtered and the solid washed with ice cold light-petroleum-benzene (1:1). The product was separated from the triethylammonium hydrochloride by washing the solid with cold chloroform and filtering. The filtrate was washed once with an equal volume of water. After drying it over anhydrous magnesium sulphate, the chloroform was stripped off, leaving a solid residue (11.6 g, 50%) of N,N-dimethyl-N'-trichloroacetylurea, m.p. 149-151°. Recrystallisation from benzene, followed by a second recrystallisation from ether-ethanol (2:1) gave the pure compound, m.p. 151-153°, (7.6 g, 33%). (Found: C, 26.07; H, 3.30; Cl, 45.29; N, 11.67. $C_5H_7Cl_3N_2O_2$ requires C, 25.72; H, 3.02; Cl, 45.56; N, 12.00 %).

(g) N'-Dichloroacetyl-N,N-dimethylurea

This was made in a two step procedure from dichloroacetamide, but without isolation of the intermediate dichloroacetyl isocyanate.



The isocyanate was made by the method described for monochloroacetyl isocyanate.⁵⁰

To a stirred mixture of dichloroacetamide (12.8 g, 0.1 mole) in ethylene dichloride (50 ml) cooled to 0°, was added oxalyl chloride (13 g, 0.1 mole) in one lot. The mixture was refluxed until the evolution of hydrogen chloride ceased (five hours). After cooling the reaction to 0° in an ice-salt bath, a solution of dimethylamine (7 g, 0.15 mole) in ethylene dichloride (35 ml) was added dropwise, with stirring. The reaction was then left to warm to room temperature before the product was precipitated by addition of light petroleum and cooling. The solid was filtered and recrystallised from benzene (7.7 g, 39%, m.p. 115-120°). After a second recrystallisation from chloroform-light petroleum (2:1) the pure N'-dichloroacetyl-N,N-dimethylurea melted at 127-129°. The yield was 4.7 g, (24%). (Found: C, 30.39; H, 4.00; Cl, 35.57; N, 13.70. $\text{C}_5\text{H}_8\text{Cl}_2\text{N}_2\text{O}_2$ requires C, 30.17; H, 4.05; Cl, 35.63; N, 14.07%).

(h) N,N-Dimethyl-N'-deutero-N'-trichloroacetylurea

N,N-Dimethyl-N'-trichloroacetylurea (2 g) dissolved in chloroform (30 ml) was shaken with deuterium oxide for thirty minutes. After separating the two layers and drying the chloroform over anhydrous magnesium sulphate, the process was repeated. Removal of the chloroform under reduced pressure gave the required product in which at least 90% of the N-H had been exchanged (NMR). The compound was dried and stored in a vacuum desiccator over phosphorus pentoxide.

Acylated Thioureas.

The most convenient method of preparing these compounds was by direct N-acylation of the thiourea using the appropriate anhydride.

(a) Trichloroacetylthiourea

This was prepared in 60% yield, m.p. 143-145° by refluxing a benzene solution of equimolar amounts of thiourea and trichloroacetic anhydride for one hour. The product crystallised from the reaction mixture on cooling. Recrystallisation from benzene gave trichloroacetylthiourea m.p. 144-145°. (Lit.⁵¹ 145-146°). IR (nujol): ν_{\max} 1725 (C=O), 1615 and 1520 cm^{-1} .

(b) Dichloroacetylthiourea

To a stirred mixture of thiourea (3.8 g, 0.05 mole) in benzene (30 ml) was added dichloroacetic anhydride

(12 g, 0.05 mole) in benzene (10 ml) over thirty minutes. Stirring was continued for a further hour. Sufficient ether was then added to dissolve the product, and the solution was washed with water (x5). After drying with anhydrous magnesium sulphate and distilling most of the solvent off under reduced pressure, 6 g of very crude product was precipitated. This was separated by filtration and washed with hot light petroleum-benzene (1:1). The remaining solid recrystallised from chloroform-light petroleum (1:1) giving 1.8 g, (20%) of dichloroacetylthiourea, m.p. 119-120°. IR (nujol): ν_{\max} 1720 (C=O), 1620 and 1535 cm^{-1} . (Found: C, 19.44; H, 2.3; N, 14.74; S, 17.12. $\text{C}_3\text{H}_4\text{Cl}_2\text{N}_2\text{OS}$ requires C, 19.26; H, 2.14; N, 14.98; S, 17.12%).

(c) N-Ethyl-N-trichloroacetylthiourea

Ethylthiourea (5.2 g, 0.05 mole) was partially dissolved in benzene (50 ml) by warming. To this stirred mixture was added trichloroacetic anhydride (15.4 g, 0.05 mole) over thirty minutes. The reaction was left stirring for four hours then diluted with benzene (150 ml) and washed with water (100 ml x 5). After drying over anhydrous magnesium sulphate, all but the last 5-10 ml of benzene was distilled off under reduced pressure. The product crystallised from this concentrated solution upon standing, m.p. 82.5-83.5°. The yield was 9.6 g (77%). IR (nujol): ν_{\max} 1705 (C=O), 1550 and 1510 cm^{-1} .

NMR (CDCl_3); δ 3.73 ppm. (2 protons, multiplet, $\text{NH}-\text{CH}_2$)
 (Found: C, 24.34; H, 2.93; N, 11.07; S, 12.96.

$\text{C}_5\text{H}_7\text{Cl}_3\text{N}_2\text{OS}$ requires C, 24.07; H, 2.83; N, 11.23; S, 12.85%).

(d) N-Dichloroacetyl-N'-ethylthiourea

This was prepared from the reaction of ethylthiourea with dichloroacetic anhydride in benzene using the method described above for N-ethyl-N'-trichloroacetylthiourea except that larger amounts of water (250 ml x 6) were necessary to remove the dichloroacetic acid from the reaction mixture. The product crystallised from a few ml of benzene to give a yield of 6.2 g (58%) m.p. 108-110°. Two further recrystallisations from light petroleum-benzene (1:1) gave a sample for analysis, m.p. 110-111°. IR (nujol); ν_{max} 1705 (C=O), 1570 and 1540 cm^{-1} . NMR (CDCl_3); δ 6.44 (1 proton, singlet, Cl_2CH), 3.73 ppm (2 protons, multiplet, $\text{NH}-\text{CH}_2$). (Found: C, 27.97; H, 3.84; N, 12.74; S, 14.92. $\text{C}_5\text{H}_8\text{Cl}_2\text{N}_2\text{OS}$ requires C, 27.92; H, 3.75; N, 13.03; S, 14.91%).

(e) N-Trichloroacetyl-N,N',N'-triethylthiourea

The triethylthiourea used in this and the following preparation was made from ethylisothiocyanate and diethylamine as described in the literature for the preparation of methylthiourea.⁶⁴

N-Trichloroacetyl-N,N',N'-triethylthiourea was prepared by the reaction of triethylthiourea with a small

excess of trichloroacetic anhydride in benzene using the same method as that used for N-ethyl-N'-trichloroacetylthiourea. The crude product obtained was dissolved in light petroleum, separated from some insoluble oil, and left in the freezer to crystallise. The yield was 10.8 g (70%) m.p. 49-52°. A second crystallisation from light petroleum gave 7.7 g (50%) of pure compound, m.p. 52-54°. This was stored in the freezer. IR (nujol): ν_{max} 1685 (C=O), 1510 cm^{-1} . NMR (CCl_4): δ 4.19 (N-CH₂), 3.76 ppm (N'-CH₂). (Found: C, 35.83; H, 5.22; N, 8.77; S, 10.59. $\text{C}_9\text{H}_{15}\text{Cl}_3\text{N}_2\text{OS}$ requires C, 35.36; H, 4.95; N, 9.17; S, 10.49%).

(f) N-Dichloroacetyl N,N',N'-triethylthiourea

This was prepared in 45% yield, m.p. 39-41° from the reaction of triethylthiourea with a small excess of dichloroacetic anhydride in benzene as described for N-dichloroacetyl-N'-ethylthiourea. The crude oily compound was crystallised twice from light petroleum-ether (3:1). IR (nujol): ν_{max} 1680 (C=O) and 1505 cm^{-1} NMR (CCl_4): δ 6.62 (1 proton, singlet, Cl_2CH), 3.73 ppm (6 protons, broad peak, CH₂). (Found: C, 40.37; H, 6.01; N, 9.90; S, 12.11. $\text{C}_9\text{H}_{16}\text{Cl}_2\text{N}_2\text{OS}$ requires C, 39.86; H, 5.95; N, 10.33; S, 11.82%).

Acylated Isothioureas.

The free base forms of two isothiourea derivatives were made by S-alkylation of the corresponding thiourea

with ethyl iodide-triethylamine.

(a) N,S-Diethyl-N'-trichloroacetylthiourea

N-Ethyl-N'-trichloroacetylthiourea (4.5 g, 0.018 mole) was added to a mixture of ethyl iodide (12 ml, 0.072 mole) and triethylamine (10.6 ml, 0.072 mole). The reaction was stirred at room temperature for three hours before being shaken up with benzene (100 ml) and filtered. The benzene was then stripped from the filtrate under reduced pressure. The oily residue was crystallised from pentane (10 ml) giving the desired product. The yield was 4.2 g, (84%) m.p. 35-38°. Two recrystallisations from pentane gave the pure compound, m.p. 37.5-38.5°. IR (nujol): ν_{\max} 1630 (C=O conj.) and 1560 cm^{-1} . NMR (CCl_4): δ 3.40 (multiplet, $\text{NH}-\text{CH}_2$), and 3.16 ppm (quartet, $J=7$ cps, $\text{S}-\text{CH}_2$). (The multiplet at 3.40 collapsed to a quartet on shaking with D_2O). (Found: C, 30.60; H, 4.25; N, 9.81; S, 11.70. $\text{C}_7\text{H}_{11}\text{Cl}_3\text{N}_2\text{OS}$ requires C, 30.29; H, 3.99; N, 10.09; S, 11.55%).

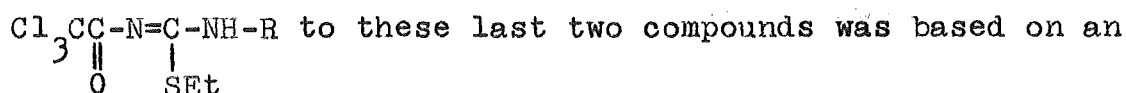
(b) S-Ethyl-N-trichloroacetylthiourea

This was prepared from trichloroacetylthiourea by the above procedure. Stripping off the benzene from the reaction mixture left a solid which, when recrystallised from chloroform, gave 40% yield of compound, m.p. 120-121°. An analytically pure sample had m.p. 124-125°. IR (nujol): ν_{\max} 1640 (C=O conj.) and 1610 cm^{-1} . NMR (CDCl_3): δ 3.23 ppm (2 protons, quartet, $J=7$ cps, $\text{S}-\text{CH}_2$). (Found:

C, 24.44; H, 3.05; Cl, 43.02; N, 10.99; S, 12.90.

$C_5H_7Cl_3N_2OS$ requires C, 24.07; H, 2.83; Cl, 42.62; N, 11.23; S, 12.85%).

The assignment of isothioureia structures, i.e.



IR and NMR comparison with N-alkyl-N-trichloroacetylthioureas.

The characteristic differences were, the IR carbonyl absorption shift to lower energy, suggesting conjugation, and the position of the methylene protons in the NMR.

Those attached to the sulphur atom absorbed at a higher field than those attached to either of the two nitrogen atoms.

Acylated Amides.

(a) N-Chloroacetyl-trichloroacetamide

A mixture of trichloroacetic acid (16.3 g, 0.1 mole) and chloroacetonitrile (8 g, 0.1 mole) was heated for 1.5 hours at 140°. The solid product on recrystallisation from ligroin-benzene (9:1) gave N-chloroacetyl-trichloroacetamide, 16 g, (67%) m.p. 95-97°. (Lit.⁵² 96°).

(b) N-Chloroacetyl-dichloroacetamide

This was prepared in 50% yield, m.p. 100-102°, by heating equimolar amounts of dichloroacetic acid and chloroacetonitrile for two hours at 140° and recrystallising the crude product from ligroin-benzene (2:1). (Lit.⁵²

m.p. 98°).

(c) N-Acetyl-N-methyldichloroacetamide

Dichloroacetyl chloride (14.8 g, 0.1 mole) was reacted with N-methylacetamide (7.3 g, 0.1 mole) in trichloroethylene (60 ml) by heating under reflux until the evolution of hydrogen chloride ceased (3 hr). The reaction was then washed with water (100 ml x 3) and dried over anhydrous sodium sulphate. After removing the solvent, the residue was distilled through a 10 cm Vigreux column and pure compound collected at 88-92° (1 mm). The yield was 9 g, (49%). (Found: C, 33.04; H, 4.19; N, 7.73. $C_5H_7Cl_2NO_2$ requires C, 32.63; H, 3.83; N, 7.61%).

N-Acetyldichloroacetamide and N-acetyltrichloroacetamide are not known compounds. Attempts to make them by the methods used above all failed.

Acylated Carbamates.

(a) Ethyl N-Dichloroacetylcarbamate

Equimolar amounts of urethane and dichloroacetyl chloride were heated on a steam bath for two hours. Recrystallisation of the solid product from benzene-light petroleum (1:1) gave an 82% yield of ethyl N-dichloroacetylcarbamate, m.p. 92-94°. Two more recrystallisations gave a sample for analysis with m.p. 93.5-94.5°. (Found: C, 30.30; H, 3.53; N, 6.47. $C_5H_7Cl_2NO_3$ requires C, 30.02; H, 3.53; N, 7.00%).

(b) Ethyl N-Methyl-N-dichloroacetylcarbamate

This was prepared by dissolving N-methylurethane (20.6 g, 0.2 mole) in trichloroethylene (20 ml) containing dichloroacetyl chloride (31 g, 0.21 mole) and refluxing the mixture until the evolution of hydrogen chloride ceased (six hours). The solvent was then removed under reduced pressure and the product was distilled through a 10 cm Vigreux column. Ethyl N-methyl-N-dichloroacetylcarbamate was collected at 85-88° (0.05 mm). The yield was 31.4 g, (73%). (Found: C, 33.96; H, 4.38; Cl, 32.87. $C_6H_9Cl_2NO_3$ requires C, 33.67; H, 4.24; Cl, 33.13%).

Other Acyl Compounds.(a) Phenyl trichloroacetate

This was prepared by heating an equimolar mixture of trichloroacetyl chloride and phenol under reflux for four hours. Purification was effected by distillation through a 25 cm fractionating column, packed with glass helices and collecting the acetate at 105°. (ca 6-10 mm). (Lit.⁵³ b.p. 125-126°/ 14 mm).

(b) Phenyl dichloroacetate

An equimolar mixture of phenol and dichloroacetyl chloride were heated under reflux for four hours. The product after two recrystallisations from light petroleum melted at 47-48.5°. (Lit.⁵⁴ 48.5-49.5°)

(c) 2,2,2-Trichloroacetophenone

Trichloroacetyl chloride (12 g, 0.066 mole) was added with stirring to aluminium chloride (8.8 g, 0.066 mole) in benzene (25 ml). This was warmed gently for one hour. The reaction was then cooled and poured onto a mixture of concentrated hydrochloric acid (40 ml) and ice (40 g) with stirring. After diluting with benzene (100 ml), the organic layer was separated, washed with water (100 ml x 2) and dried over anhydrous magnesium sulphate. The benzene was then removed and the residue was distilled to give 9 g, (56%) of 2,2,2-trichloroacetophenone b.p. 90° (1 mm). (Lit.⁵² b.p. 145° / 25 mm).

(d) 2,2-Dichloroacetophenone

This was obtained in 80% yield b.p. $105-106^{\circ}$ (4-5 mm) by chlorinating acetophenone in acetic acid, as described by Aston.⁵⁵ (Lit.⁵⁵ b.p. $132-134^{\circ}$ / 13 mm).

Dibenzoylmethane Derivatives.

(a) Bromodibenzoylmethane

Dibenzoylmethane (46 g, 0.21 mole) was dissolved in chloroform (100 ml) and cooled in an ice bath. Bromine (37 g, 0.23 mole) was added dropwise over one hour. During the addition, and for three hours after it was complete, nitrogen was continuously bubbled through the solution. After this time the solution was poured into a beaker and the chloroform was allowed to evaporate in a current of air.

The remaining solid was recrystallised from chloroform-light petroleum to give bromodibenzoylmethane. The yield was 45 g, (72%), m.p. 91-93°. (Lit.⁵⁶ 93°).

(b) Chlorodibenzoylmethane

Sulphuryl chloride (7.7 g, 0.057 mole) was added to a stirred solution of dibenzoylmethane (11.2 g, 0.05 mole) in benzene (15 ml). After eighteen hours at room temperature the benzene was stripped off. The remaining solid was recrystallised from methanol (40 ml) to give 11 g, (82%) of chlorodibenzoylmethane, m.p. 86-88°. (Lit.⁵⁷ 87-88°).

(c) Chlorotribenzoylmethane

Tribenzoylmethane was prepared in 50% yield, m.p. 220-222° by the procedure of Beringer et. al.⁵⁸ and used without the further purification necessary to raise the melting point to 237-238° (Lit.⁵⁸ 225-226° crude, 237-238° after several recrystallisations from acetonitrile).

This tribenzoylmethane was converted to chlorotribenzoylmethane in 80% yield, m.p. 122-124° by the action of chlorine as described by Kohler and Potter.⁵⁹ (Lit.⁵⁹ m.p. 122°)

Other Compounds Used for Identification Purposes.

(a) O,O-Diethyl N-Phenyl Phosphoramidate

Addition of aniline (1.9 g, 0.02 mole) to an ether solution (20 ml) of diethyl phosphorochloridate (1.7 g,

0.01 mole) resulted in the precipitation of aniline hydrochloride. After one hour the mixture was filtered and the filtrate washed with water. The ether was removed under reduced pressure, leaving a solid which after recrystallisation from benzene-light petroleum gave 1.6 g (70%) of the phosphoramidate, m.p. $78-86^{\circ}$. Further recrystallisations raised the m.p. to $90-92^{\circ}$ (Lit.⁵³ 93°).

(b) Diethyl Phenyl Phosphate

Diethyl phosphorochloridate (5.2 g, 0.03 mole) and phenol (2.8 g, 0.03 mole) were dissolved in benzene (20 ml) containing pyridine (2.4 g, 0.03 mole). The mixture was allowed to stand four days at room temperature. After the pyridine hydrochloride had been removed by filtration the filtrate was distilled under reduced pressure to give diethyl phenyl phosphate, b.p. 100° (0.2-0.1 mm). (Lit.⁵³ $200-230^{\circ}/70$ mm).

(c) O,O-Diethyl S-Phenyl Phosphorothiolate

Phenylsulphenyl chloride, prepared from thiophenol and sulphuryl chloride, was reacted with triethyl phosphite using the procedure of Morrison,⁶⁰ to give the phosphorothiolate, b.p. 120° (0.5 mm). (Lit.⁶⁰ $182-186^{\circ}/30$ mm)

(d) Diethyl 2-Acetyl-1-methylvinyl Phosphate

3-Chloropentane-2,4-dione was prepared by chlorination of pentane-2,4-dione (25 g, 0.25 mole) dissolved in benzene

(25 ml), by the slow addition, with stirring, of sulphuryl chloride (33 g, 0.25 mole). The addition was carried out at room temperature and after it was completed, the reaction mixture was distilled under reduced pressure.

3-Chloropentane-2,4-dione was collected at 76-78° (ca 60 mm) (Lit.⁵³ b.p. 156°/760 mm).

Reaction of this with triethyl phosphite, as described by Pudovik,⁶¹ gave diethyl 2-acetyl-1-methylvinyl phosphate, b.p. 90-92° (0.5 mm). (Lit.⁶¹ 119-120°/2 mm) NMR (CCl₄): δ 6.22 and 5.44 ppm (1 proton, singlets, C=CH).

(e) Diethyl 2,2-Dichloro-1-phenylvinyl Phosphate

This was prepared from 2,2,2-trichloroacetophenone and triethyl phosphite using the procedure of Kharasch and Bengelsdoff.²⁹ The yield was 70%, b.p. 130-135° (0.5 mm). (Lit.²⁹ 105-110/10⁻³ mm)

(f) Diethyl 2-Chloro-1-phenylvinyl Phosphate

2,2-Dichloroacetophenone was reacted with triethyl phosphite as described by Pudovik and Biktimirova⁶² to give a 70% yield of diethyl 2-chloro-1-phenylvinyl phosphate, b.p. 140-145° (1 mm). (Lit.⁶² 139-140°/0.5 mm) NMR (CCl₄): δ 6.52 and 6.22 ppm (1 proton, singlets, C=CH).

(g) Diethyl 2,2-Dichloro-1-phenoxyvinyl Phosphate

Phenyl trichloroacetate was reacted with triethyl phosphite using the method of Nishizaw and Mitzutani⁶³ to give a 60% yield of the vinyl phosphate, b.p. 145-148° (0.5 mm), n_D^{20} 1.5024. (Lit.⁶³ b.p. 154-156°/0.9 mm,

³³_n 1.4966)
D

(h) Diethyl 2,2-Dichloro-1-(N,N'-dimethylureido)vinyl Phosphate

Triethyl phosphite was reacted with N,N'-dimethyl-N-trichloroacetylurea in benzene by heating the solution for two hours under reflux ^{39a}. After the benzene had been removed under vacuum, the oily residue was distilled to give the vinyl phosphate, b.p. 100-110° (0.1 mm). NMR (CCl₄): δ 6.0 (1 proton, singlet, N'-H), 4.13 (4 protons, multiplet, P-O-CH₂), 2.92 (3 protons, singlet, N-CH₃), 2.76 (3 protons, doublet, J=4 cps, N'H-CH₃) and 1.37 ppm (6 protons, triplet, C-CH₃).

Reactions of α -Halogenocarbonyl compounds with Triethyl Phosphite.-

Introduction.

Preliminary investigations using trichloroacetylurea and trichloroacetylthiourea showed that the reactions of the system Cl_3CCONHR , where R is an electron-withdrawing group, i.e. CO-X , CS-X were complex and did not appear to give either enol phosphates or vinylamine derivatives. The major product obtained in both cases was the corresponding dichloroacetyl compound. From the other products obtained it appeared that attack on halogen was occurring and the enolate anion was being protonated by the acidic imide hydrogen of the starting material. In order to verify this, reactions were carried out in a variety of protolytic solvents. Simple kinetics studies on this type of reductive dehalogen reaction were also undertaken in order to gain an understanding of the factors involved.

On finding that this reductive dehalogenation had a first-order dependence on the concentration of acidic proton source, many of the reactions were repeated under dilute conditions in the hope that the acidic proton of the starting material would no longer interfere. New compounds, vinyl phosphonates, were produced under these conditions. These products were found to require a two molar ratio of triethyl phosphite to amide and whereas they

may have been present as minor products before, they could now be obtained in good yields.

Some N-substituted dichloroacetamide derivatives also reacted in a similar way and so it was of interest to investigate the reactions of the corresponding N,N-disubstituted dichloroacetamides as potential sources of enol phosphates.

Other reductive dehalogenation reactions mentioned in the literature (see P. 26) are claimed to occur by a free radical mechanism. Some of these reactions were reinvestigated with the aim of verifying this, or showing that it occurred by protonation of the enolate anion. It was also necessary to show that the dehalogenation observed in this work did not occur by a free radical mechanism.

Note. In general the yield of a reaction was determined from the weights of the products isolated. However, when there was more than one major product, the amounts isolated did not necessarily give a true indication of the relative yields. In such cases where it was desirable to have an accurate estimate of the yields these were determined by one of the following methods of analysis.

1. Gas-Liquid Chromatography

This was carried out by the usual method of adding an internal standard to the reaction mixture and measuring the area under the peaks of the chromatogram. The detector response was calibrated with standard solutions

of the pure compounds and internal standard, immediately before the reactions were analysed.

2. NMR Spectrometry

This was achieved by carrying out the reaction on about a milli-molar scale, removing the solvent, if any, under vacuum, and then adding from a stock solution one proton equivalent, i.e. $\frac{1}{3}$ m-mole of acetonitrile in 1 ml of carbontetrachloride. An integral of the NMR spectrum could then be used to determine the yield of any products which had distinct peaks whose integral could be compared with that of CH_3CN at 1.98 ppm, the integral of this peak being taken as equivalent to one proton. The protons most often used for this purpose were the dichloroacetyl, $\text{Cl}_2\text{CHCO}-$, and olefinic protons. It was not always necessary to add the internal standard, as a group of peaks already present could be used. This was often the case when aromatic compounds were involved.

Compounds isolated from reactions were identified, if known compounds, by comparison with authentic samples. This means that, for liquids, the GLC retention times and IR spectra were identical; and for solids, the IR spectra were identical, and the melting point of the compound was not depressed when mixed with an authentic sample. New compounds were characterised by micro analyses as well as physical methods such as NMR, IR, and, in isolated cases, mass spectrometry was used.

Reaction of Chloroacetylurea with Triethyl Phosphite.

Chloroacetylurea (4.1 g, 0.03 mole) and triethyl phosphite (5.2 g, 0.031 mole) were heated at 150-160° with stirring. The chloroacetylurea dissolved after about ten minutes. After forty-five minutes the reaction was cooled and dissolved in ethanol. The compound that crystallised from the solution was collected by filtration to give 4.1 g (58%) of diethyl ureidocarbonylmethylphosphonate, $(\text{EtO})_2\text{P}(\text{O})-\text{CH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NH}_2$, m.p. 121.5-122°. (Found: C, 35.03; H, 6.35; N, 11.65; P, 12.3. $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_5\text{P}$ requires C, 35.30; H, 6.35; N, 11.76; P, 13.0%). NMR (CDCl_3): δ 11.1, 7.96 and 6.44 (1 proton each, singlets, N-H), 4.16 (4 protons, multiplet, P-O-CH₂), 3.12 (2 protons, doublet, J=22 cps, P-CH₂), and 1.37 ppm (6 protons, triplet, J=7 cps, C-CH₃).

The methylene multiplet at δ 4.16 ppm was characteristic of the P-O-CH₂-CH₃ group and was observed in all of the O-ethyl phosphorus acid derivatives studied. It can be explained as a simple A₂B₃X system of spin-spin interaction, where $J_{\text{AB}}=7$ cps, $J_{\text{BX}}=8$ cps, i.e. the multiplet is approximately a quintet.

The phosphonate obtained here was the product expected for an Arbusov reaction and in this respect chloroacetylurea behaves as other chloroacetic acid derivatives do e.g. amide, ester. Consequently this reaction will not be discussed further.

Reaction of Trichloroacetylurea with Triethyl Phosphite.

This reaction was studied under three sets of conditions. Firstly, with a convenient volume of inert solvent, secondly, with a large volume of inert solvent and a two molar ratio of phosphite, and finally, in the presence of an added protic species (phenol) in an attempt to increase the yield of dichloroacetylurea.

(a) Trichloroacetylurea (2.04 g, 0.01 mole) was reacted with triethyl phosphite (1.7 g, 0.01 mole) in benzene (6 ml) by heating the mixture under reflux for two hours. On cooling the solution a solid crystallised out and was filtered off. This crude material (0.72 g), on recrystallisation from ethanol gave 0.4 g (23%) of product m.p. 149-150°. The product was identified as dichloroacetylurea (Lit. ⁴⁸ m.p. 152-154°) by comparison with an authentic sample.

The filtrate of the reaction mixture gave on distillation under reduced pressure, a clear liquid (0.5 g), b.p. 110-130° (ca 20 mm). This was identified by IR and GLC retention time as triethyl phosphate. The GLC trace of the distillate also showed the presence of diethylphosphorochloridate in small amounts (5-10%) (identified by the retention time of the peak and from the fact that it disappeared on the addition of excess of aniline with the appearance of another peak whose retention time was identical with diethyl N-phenyl phosphoramidate).

(b) Trichloroacetylurea (1.02 g, 0.005 mole) and triethyl phosphite (1.7 g, 0.01 mole) were added to benzene (70 ml). Complete reaction of the two was achieved by refluxing the mixture for four hours, the progress of the reaction being followed by TLC. All but the last few ml of benzene was then removed under reduced pressure and the residue adsorbed onto a silica column (50 g). Ether-methanol (4:1) eluted 0.72 g of a solid which was crystallised from ether-methanol (7:1) to give a compound m.p. 155-158°. This was identified as diethyl 2,2-dichloro-1-ureidovinylphosphonate, $(\text{EtO})_2\text{P}(\text{C}=\text{CCl}_2)\text{NHCONH}_2$ (0.3 g, 20%)

which after recrystallisation had the m.p. 157-158°. IR (nujol): ν_{max} 3400, 3180 and 3160 (N-H), 1665 (C=O), 1625 and 1530 (N-H), 1580 (C=C), 1242 cm^{-1} (P=O). NMR (CDCl_3): δ 7.9 (1 proton, doublet, $J=2$ cps, P-C-NH), 6.23 (2 protons, singlet, NH_2), 4.25 (4 protons, multiplet, $J=7$ cps, P-O-CH₂), 1.38 ppm (6 protons, triplet, $J=7$ cps, C-CH₃). (Found: C, 29.26; H, 4.60. $\text{C}_7\text{H}_{13}\text{Cl}_2\text{N}_2\text{O}_4\text{P}$ requires C, 28.88; H, 4.50%).

Earlier elutions with less polar solvents were combined and distilled to give 0.77 g (85%) of triethyl phosphate.

(c) Phenol (4.7 g, 0.05 mole) was dissolved in benzene (40 ml) trichloroacetylurea and triethyl phosphite (4.5 g, 0.027 mole) were then added, and the mixture was heated with stirring for one hour at 60°. After cooling the solution in ice, it was filtered to give 3.6 g (85%) of

dichloroacetylurea, m.p. 148-151°.

The filtrate was concentrated and distilled at 0.1 mm through a 10 cm Vigreux column. The first liquid fractions collected were triethyl phosphate and mixtures of triethyl phosphate with diethyl phenyl phosphate. The final fraction collected (b.p. 100-110°) was mainly diethyl phenyl phosphate, 2.6 g(45%), identified by a comparison with an authentic sample.

Reaction of N,N-Dimethyl-N'-trichloroacetylurea with Triethyl Phosphite.

This reaction was also investigated in an inert solvent at two different concentrations. In the more dilute reaction a two molar ratio of phosphite was used. A third reaction with deuterated starting material was studied in an attempt to locate the origin of the proton contained in the dichloroacetyl product.

(a) N,N-dimethyl-N'-trichloroacetylurea (4.7 g, 0.02 mole) was added to triethyl phosphite (3.4 g, 0.02 mole) in benzene (5 ml). The mixture was stirred and heated to 80°. An exothermic reaction followed. The heat was removed once this started, and after the reaction had subsided, the mixture was held at 80° for thirty minutes. The benzene was then removed under reduced pressure and 50 ml carbon tetrachloride-light petroleum (4:1) was added. After this solution had been left in the freezer for several hours, a crystalline compound was filtered off. This

proved to be N'-dichloroacetyl-N,N-dimethylurea, m.p. 125-127°, identified by comparison with an authentic sample. The yield was 0.89 g (22%).

The filtrate was evaporated down under reduced pressure and distilled at 0.5 mm until the temperature of the distillate started to rise above 55°. The distillate collected at 50-55° was triethyl phosphate, 1.2 g (32%).

The undistilled residue from the distillation was adsorbed on to a silica column (100 g). Benzene-ether (9:1) eluted unreacted starting material (11%) (0.5 g, m.p. 140-148°). A second solid was eluted with benzene-ether (4:1). This was more of the product N'-dichloroacetyl-N,N-dimethylurea 0.6 g, (15%) (m.p. 126-128° after recrystallisation). Finally, elution with pure ether gave a compound, 0.5 g, subsequently (see following experiment) identified as the vinyl phosphonate, $(\text{EtO})_2\text{P}-\text{C}(\text{NHCONMe}_2)=\text{CCl}_2$. The yield was 8%

of theory. No other products could be positively identified in the remaining 4 g of material which was eluted from the column. No significant amount was in any one fraction.

(When this reaction was first investigated 24 ml of benzene were used and similar yields were obtained i.e. $\text{Cl}_2\text{CHCONHCONMe}_2$ 35%, vinyl phosphonate 16%, and triethyl phosphate 40%. Decreasing the amount of benzene beyond

this point appears to have had little effect on the product ratios, probably because of a limit to the solubility of the starting material in benzene).

(b) N,N-Dimethyl-N'-trichloroacetylurea (2.34 g, 0.01 mole) and triethyl phosphite (3.4 g, 0.02 mole) were dissolved in benzene (120 ml) and heated under reflux for four hours.

The benzene was then removed by distillation under reduced pressure and the residue crystallised from chloroform-light petroleum (1:3) to give 1.6 g (50%) of diethyl 2,2-dichloro-

1-(N',N'-dimethylureido)vinylphosphonate (EtO) $\begin{array}{c} \text{P}-\text{C}=\text{CCl}_2 \\ \parallel \quad | \\ \text{O} \quad \text{NHCONMe}_2 \end{array}$,
m.p. 147-149°. A further recrystallisation

from benzene-light petroleum (1:1) gave the pure compound,

m.p. 151-152°. IR (nujol): $\overset{\text{max}}{\vee}$ 3250 (N-H), 1650 (C=O), 1575 (C=C), 1520 (N-H) and 1270 cm^{-1} (P=O). NMR (CDCl_3):

δ 6.28 (1 proton, doublet, $J=6$ cps, N-H), 4.12 (4 protons, multiplet, P-O-CH₂), 2.90 (6 protons, singlet, N-CH₃),

1.34 ppm (6 protons, triplet, $J=7$ cps, C-CH₃). (Found:

C, 33.77; H, 5.41; N, 8.47; P, 8.08. $\text{C}_9\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_4\text{P}$ requires
C, 33.87; H, 5.37; N, 8.78; P, 9.71%).

The filtrate, after the solvent had been stripped off, was distilled to give 1.52 g (83%) of triethyl phosphate.

Reaction of N'-deutero-N,N-dimethyl-N'-trichloroacetylurea with Triethyl Phosphite

N'-D-N,N-Dimethyl-N'-trichloroacetylurea (less than 10% N-H present) (1.16 g, 0.005 mole) was reacted with triethyl phosphite (1 g, 0.066 mole) in benzene (6 ml) by heating the mixture under reflux for two hours. Light petroleum (10 ml) was then added and the reaction left in the freezer overnight. The solid that crystallised out was collected by filtration and washed with chloroform-pentane (1:2). (The washings contained 0.24 g (15%) of the crude vinyl phosphonate). After being washed, the remaining solid, 0.06 g, m.p. 124-126°, was combined with a second crop of crystals obtained from the mother liquor by concentrating it, adding more pentane and leaving it in the freezer for 2-3 days. This gave a total yield of 0.16 g (16%) of N'-D-N,N-dimethyl-N'-(α -D- α,α -dichloroacetyl)urea. NMR (CDCl_3) showed that there was less than 10% of the undeuterated product present (δ 6.60 ppm Cl_2CH). IR (nujol): 2230 cm^{-1} (C-D).

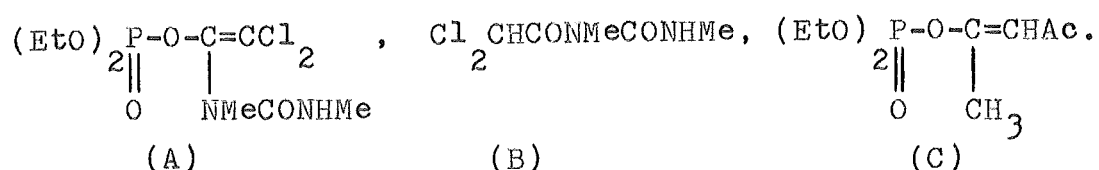
Reaction of N,N'-Dimethyl-N-trichloroacetylurea with Triethyl Phosphite in Protic Solvents.

Ethanol could not be used as a solvent as it led to solvolysis of the acyl urea.

(a) Reaction in 1,2-dimethoxyethane-acetylacetone.

N,N'-Dimethyl-N-trichloroacetylurea (0.3 g,

0.0013 mole) was dissolved in dimethoxyethane (1.5 ml) and acetylacetone (0.5 ml 0.005 mole) was added followed by triethyl phosphite (0.24 g, 0.0014 mole). After the reaction had been refluxed for one hour the following products made up the reaction mixture ;



These were identified by GLC and NMR. By stripping off the solvent and excess acetylacetone at 10^{-2} mm pressure before running the NMR on the reaction mixture, an estimate of the ratio of these products as 2:6:5 respectively was obtained. (This same reaction with benzene as solvent gave the enol phosphate A as the major product with little more than trace amounts of B and C).

In order to ensure that the effect of the acetylacetone was not a result of transesterification of either A or triethyl phosphite the following control reactions were performed.

1. The above reaction was repeated but the addition of acetylacetone was withheld until after the reaction mixture had been refluxed for one hour. Refluxing then for a further hour with the acetylacetone present failed to produce any detectable quantities (GLC, NMR) of either of the products B or C. The enol phosphate A was the major product.

2. Similarly acetylacetone and triethyl phosphite failed to give detectable amounts of the enol phosphate C when refluxed together in dimethoxyethane for two hours.

Reaction of N-chloroacetyl-trichloroacetamide with Triethyl Phosphite.

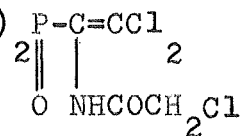
An investigation of this reaction was carried out under two sets of conditions. The first was conducted with an equimolar ratio of starting materials and in the second a two molar ratio of phosphite was used in a large excess of solvent.

(a) N-Chloroacetyl-trichloroacetamide (12 g, 0.05 mole) was dissolved in benzene (100 ml) and triethyl phosphite (9 g, 0.055 mole) added over thirty minutes at room temperature. The reaction was stirred during addition and afterwards for a further hour. The benzene was then removed under vacuum and the residue distilled at 0.1 mm pressure through a 10 cm column packed with glass helices. Triethyl Phosphate (4.1 g, 40%) was collected at 40-44°. The fraction collected at 105-111° (5.4 g) was recrystallised from ligroin-benzene (2:1) to give 4.5 g (45%) of N-chloroacetyl-dichloroacetamide m.p. 98-100°. The remainder of the reaction mixture decomposed to a black residue.

A second reaction on one-third of the previous scale was distilled until the temperature of the distillate reached 90° (0.1 mm). The residue was washed out with

benzene and adsorbed onto a silica column (50 g).

Elution with ether-benzene (1:4) gave a clear oily compound (1 g) which crystallised from light petroleum-ether (3:1) to give 0.2 g (5%) of diethyl 2,2-dichloro-1-(α -chloroacetamido)vinylphosphonate, (EtO) $\text{P}=\text{C}=\text{CCl}_2$



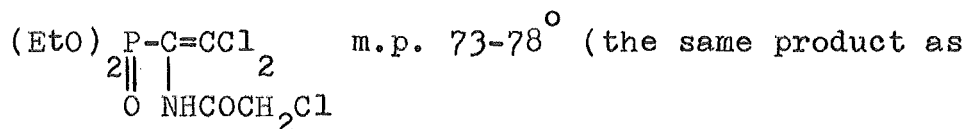
m.p. 70-77°. Further recrystallisations from ether gave an analytically pure sample m.p. 81-82°. IR (nujol):

ν_{max} 3380, 3170 (N-H), 1685 (C=O), 1578 (C=C), 1510 (N-H), 1260 and 1250 cm^{-1} . NMR (CDCl_3): δ 8.23 (1 proton, singlet, N-H), 4.2 (multiplet, P-O-CH₂), 4.13 (singlet, CH₂Cl), 1.38 ppm (6 protons, triplet, J=7 cps, C-CH₃). (Found: C, 29.69; H, 4.12; N, 4.23; P, 9.22. $\text{C}_8\text{H}_{13}\text{Cl}_2\text{NO}_4\text{P}$ requires C, 29.61; H, 4.04; N, 4.32; P, 9.54%).

(b) N-Chloroacetyl-trichloroacetamide (4.76 g, 0.02 mole) was dissolved in benzene (200 ml). Triethyl phosphite (6.9 g, 0.041 mole) was added and the reaction heated under reflux for one hour. After removing the benzene under reduced pressure the reaction was distilled at 0.5-1 mm pressure through a 10 cm Vigreux Column until the triethyl phosphate had been collected, 3.05 g, (84%) b.p. 50-55° (1mm).

The residue was washed out of the distillation flask with ether, which was then stripped off. The oily residue was dissolved in light petroleum-ether (1:1) and

left standing in the freezer for 1-2 days to crystallise. The solid was collected by filtration and washed with ice cold solvent to give 2.2 g (35%) of the vinyl phosphonate,



obtained in the previous reaction in low yield). After recrystallisation from ether, this compound had m.p. $79-81^\circ$.

Reaction of N-Chloroacetyl-dichloroacetamide with Triethyl Phosphite.

Early work on this reaction revealed that solvent was not necessary to prevent dehalogenation occurring and that some of the imide starting material was recovered when the reaction was carried out on an equimolar basis.

(a) Initially, the stoichiometry of the reaction was determined by carrying out three small scale reactions of the imide with varying ratios of triethyl phosphite to halogen derivative. A typical reaction is given below.

N-Chloroacetyl-dichloroacetamide (0.25 g, 0.0013 mole) and triethyl phosphite (0.22 g, 0.0013 mole) were heated together at 100° for two hours. After the reaction had cooled to room temperature, one proton equivalent of acetonitrile was added (see note p. 48). An NMR analysis gave the following proton integral ratio:

<u>Peak</u>	<u>Integral</u>
$\text{Cl}-\text{CHCONHCOCH}_2-\text{Cl}$ (δ 4.40ppm)	54
CH_3CN (δ 1.98ppm)	47

showing that 57% of the imide had not reacted. (A longer reaction time did not affect the extent of reaction).

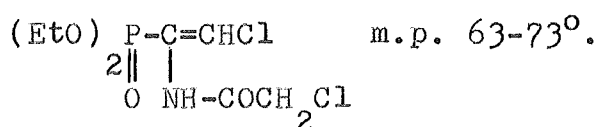
Results for three reactions were :

<u>Molar ratio</u>	<u>% imide</u>
<u>imide : triethyl phosphite</u>	<u>reacted</u>
1 : 1	43
1 : 1.5	70
1 : 2	92

These show that at least two moles of triethyl phosphite are necessary for the complete reaction of one mole of N-chloroacetyl-dichloroacetamide.

(b) A mixture of N-chloroacetyl-dichloroacetamide (4 g, 0.02 mole) and triethyl phosphite (6.9 g, 0.041 mole) was heated to 80° with stirring. Soon after the imide had dissolved an exothermic reaction took place. The heating was stopped until the reaction had subsided and then continued for an hour at 100°. The reaction mixture was distilled through a 10 cm Vigreux column as quickly as possible (once the triethyl phosphate (2.7 g, 75%) had been collected at 48-58° (1mm)). A further

0.22 g of distillate was collected between 58-140° before the main fraction of 4.9 g was distilled over at 140-160° (0.1 mm). This was dissolved in 40 ml of carbon tetrachloride-benzene-light petroleum (1:1:3) and left in the freezer to crystallise. The solid was collected by filtration to give 2.2 g (38%) of crude diethyl 2-chloro-1-(α -chloroacetamido)vinylphosphonate,



The mother liquor from this filtration was evaporated down under reduced pressure and the residue adsorbed onto a silica column (50 g). The only product identified in the fractions eluted from this was a further 0.36 g of the vinyl phosphonate, eluted with benzene-ether (1:1).

This gave a total yield of 2.56 g (44%) of the crude phosphonate which on crystallisation from ether followed by carbon tetrachloride-benzene-light petroleum had m.p. 90-91°. IR (nujol): ν_{max} 3165 (N-H), 1705 (C=O), 1600 (C=C), 1530 (N-H) and 1245 cm^{-1} (P=O). NMR (CDCl_3): δ 7.85 (1 proton, doublet, $J=5$ cps, N-H), 7.03 (1 proton, doublet, $J=8$ cps, C=CH), 4.18 (multiplet, P-O-CH₂), 4.16 (singlet, CH₂Cl) and 1.35 ppm (6 protons, triplet, $J=7$ cps, C-CH₃). (Found: C, 33.17; H, 4.84; N, 4.74; P, 10.72. $\text{C}_8\text{H}_{14}\text{ClNO}_4\text{P}$ requires C, 33.12; H, 4.86; N, 4.84; P, 10.68%).

64.

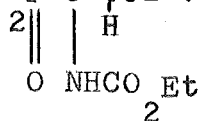
Mass spectrum M^+ 289 (6.6%) with significant peaks at m/e (%) 254 (100), 246 (6.3), 240 (3.3), 226 (25.6), 213 (39.6), 212 (5), 198 (69.2), 184 (42.9), 180 (10.7), 178 (8.8) and 166 (4.4). The peak at 289 was mass measured (within 4 pmm) and found to agree with $C_8H_4Cl_2NO_4P$.

Reaction of Ethyl N-dichloroacetylcarbamate with Triethyl Phosphite.

This reaction was conducted both in the absence of solvent and with a two molar ratio of phosphite.

Ethyl N-dichloroacetylcarbamate (4 g, 0.02 mole) and triethyl phosphite (6.9 g, 0.041 mole) were heated to 140° . Mild evolution of a gas, presumably ethyl chloride, occurred at about 130° . After two hours at 140° the reaction was distilled at 0.5mm pressure through a 10 cm Vigreux column. The liquid collected at $48-54^\circ$ was identified as triethyl phosphate (2.6 g, 72%).

The rest of the product was distilled quickly and 4.3 g of compound b.p. $100-140^\circ$ was obtained. This was adsorbed onto a silica column (100 g). Elution with benzene-ether (4:1) gave 2.2 g of a clear oily liquid, identified as diethyl 2-chloro-1-carboethoxyaminovinylphosphonate, $(EtO)_2P-C=CCl$. The yield was 40% of theory.



IR: $\sqrt{\text{max}}$ 3180 (N-H), 1730 (C=O), 1600 (C=C), 1510 (N-H) and 1240 cm^{-1} (P=O and C-O-C). NMR (CCl_4): δ 7.19 (1 proton, doublet, $J=6$ cps, N-H), 6.93 (1 proton, doublet, $J=8$ cps, C=CH), 4.17 (quartet, CO-CH₂), 4.09 (multiplet, P-O-CH₂) and 1.31 ppm (9 protons, multiplet, C-CH₃).
 (Found: C, 37.82; H, 6.20; N, 4.31; P, 11.18. $\text{C}_9\text{H}_{17}\text{ClNO}_2\text{P}$ requires C, 37.84; H, 6.00; N, 4.90; P, 10.84%).

Reaction of N-Acetyl-N-methyldichloroacetamide with Triethyl Phosphite.

An investigation of this and the following reaction was undertaken to see if a normal Perkow reaction would occur for dichloroacetic acid derivatives of this type.

Triethyl phosphite (6.4 g, 0.038 mole) was added to N-acetyl-N-methyldichloroacetamide (5.9 g, 0.032 mole) and the mixture was heated for one hour at 100°. The temperature was then raised to 130° and held there for two hours. Vacuum distillation through a 10 cm Vigreux column at 0.2-0.4mm afforded 7.1 g (78% of theory) diethyl 2-chloro-1-(N-methylacetamido)vinyl phosphate,

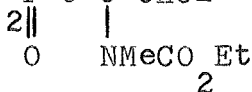
(EtO)₂P-O-C=CHCl, b.p. 120-135°. An analytically pure sample was collected at 130-135°.

IR: $\sqrt{\text{max}}$ 1690 (C=O), 1660 (C=C), 1280 cm^{-1} (P=O). NMR (CCl_4): δ 6.22 and 6.02 (1 proton, doublets, $J=2.5$ and 0 cps resp. C=CH), 4.18

(4 protons, multiplet, $J=7$ cps, $P-O-CH_2$), 3.03 (3 protons, singlet, $N-CH_3$), 2.14 and 2.10 (3 protons, singlets, $CO-CH_3$), 1.38 ppm (6 protons, triplet, $J=7$ cps, $C-CH_3$). (Found: C, 38.09; N, 6.07; Cl, 11.03. $C_{10}H_{17}ClNO_2P$ requires C, 37.84; H, 6.00; N, 4.90; P, 10.84%). Mass spectrum, M^+ 285 (0.72%) with significant peaks at m/e (%) 250 (19.4), 243 (1.05), 222 (2.08), 194 (1.83), 89 (100).

Reaction of Ethyl N-Dichloroacetyl-N-methylcarbamate with Triethyl Phosphite.

(a) Ethyl N-dichloroacetyl-N-methylcarbamate (7.9 g, 0.037 mole) and excess triethyl phosphite (7.5 g, 0.045 mole) were heated at 120° . After the gas evolution had subsided the temperature was raised to 140° for one hour. The reaction mixture was then distilled at 0.2mm pressure through a Vigreux column to give 9 g (77%) of diethyl 2-chloro-1-(N-carboethoxy-N-methylamino)vinyl phosphate, $(EtO)_2P-O-C=CHCl$, collected at $120-130^\circ$.



IR: ν_{\max} 1730 ($C=O$), 1670 ($C=C$), 1325 ($C-O-C$), 1280 cm^{-1} ($P=O$). NMR (CCl_4): δ 6.04 and 5.37 (1 proton, doublets, $J=2.5$ and 0 cps, $C=CH$), 4.14 (6 protons, multiplet, $O-CH_2$), 3.06 (3 protons, singlet, $N-CH_3$), 1.33 ppm (9 protons, multiplet, $C-CH_3$). (Found: C, 37.95; H, 6.04; Cl, 11.58; P, 9.95. $C_{10}H_{19}ClNO_2P$ requires C, 38.05; H, 6.07; Cl, 11.23; P, 9.81%).

(b) Repetition of the reaction adding a two molar ratio of phenol (in order to check whether added protic species affected enol phosphate formation) still resulted in a 50% yield of enol phosphate as was shown by an NMR analysis. The ratio of olefinic proton (δ 6.04, 5.73 ppm) to acetonitrile (δ 1.98 ppm) was 16 : 33.

Reaction of Trichloroacetylthiourea with Triethyl Phosphite.

This reaction was carried out in benzene solution and once the products had been isolated and/or identified it was repeated several times for analysis by GLC and NMR. Finally the reaction was carried out in ethanol.

(a) In benzene solution.

Trichloroacetylthiourea (5.35 g, 0.024 mole) was suspended in a solution of triethyl phosphite (4 g, 0.024 mole) in benzene (30ml). Soon a mild exothermic reaction commenced and the trichloroacetylthiourea dissolved. After standing for one hour, 5 ml of light petroleum was added and the mixture was chilled for several hours in a freezer. A compound crystallised out and was collected by filtration. This proved to be dichloroacetylthiourea (0.85 g, 18%), m.p. 117-119^o; identified by comparison with an authentic sample.

The filtrate was evaporated down under reduced pressure and the oily residue left in the freezer for three days. After decanting the oil from the crystals, they were washed with light petroleum-ether (3:1) and

then crystallised from this solvent to give 0.34 g (6%) of S-ethyl-N-trichloroacetylthiourea m.p. 119-122°. Recrystallisation from chloroform raised the m.p. to 124-125°. This was not depressed when mixed with an authentic sample.

Repetition of this reaction on a milli-molar scale for NMR analysis indicated that dichloroacetylthiourea and S-ethyl-N-trichloroacetylthiourea were actually produced in the reaction in yields of 66% and 32% respectively. The peaks at δ 6.49 ($\text{Cl}_2\text{CH}-$), 3.23 ($\text{S}-\text{CH}_2$), and 1.98 ppm (CH_3-CN) were in the ratio 37 : 36 : 56 respectively.

The two major volatile products of this reaction were identified as triethyl phosphate and diethyl phosphorochloridate (subsequently converted to phosphoramidate) by GLC. Small amounts of unreacted triethyl phosphite were also detected in the reaction mixture. To obtain an estimate of the yields of these two products, a quantitative GLC analysis of the reaction was carried out using n-tridecane as an internal standard.

(b) The reaction (a) above was repeated using 2.5 milli-mole of trichloroacetylthiourea and triethyl phosphite. n-Tridecane (0.27 milli-mole in 10 ml of benzene) was added at the end of the reaction. Samples of this were then analysed by GLC under the same conditions that

were used for calibration of the detector*. The following results were obtained.

<u>Compound</u>	<u>Av. peak</u> <u>ratio</u>	<u>Calibration</u> <u>response/mole</u>	<u>m-moles</u> <u>present</u>	<u>% yield</u>
$(\text{EtO})_2\text{P}-\text{Cl}$ $\begin{array}{c} \parallel \\ \text{O} \end{array}$	0.78	0.15	1.4	56
$(\text{EtO})_3\text{PO}$	0.50	0.37	0.36	15
n-Tridecane	1	1	0.27	

(c) Reaction in ethanol.

Trichloroacetylthiourea (0.28 g, 0.0013 mole) was dissolved in ethanol (2 ml) and triethyl phosphite (0.24 g, 0.0013 mole) added. After one hour at room temperature the reaction was analysed by NMR. The proton ratio of the peaks at δ 6.49 ($\text{Cl}_2\text{CH}-$) and 1.98 ppm (CH_3CN) was 30:36 and indicated a yield of 85% for dichloroacetylthiourea. GLC showed that triethyl phosphate was the only volatile product.

* An Aerograph Hi-Fi flame ionization detector response was calibrated for triethyl phosphate, diethyl phosphorochloridate and n-tridecane using a standard solution of the three compounds at concentrations comparable with those encountered in this reaction. A 5' column of 5% SE-30 on chromosorb W was used at an initial temperature of 70° and a programme of 6°/minute.

Reaction of N-Ethyl-N'-trichloroacetylthiourea with
Triethyl Phosphite.

(a) N-Ethyl-N'-trichloroacetylthiourea (1.2 g, 0.005 mole) was dissolved in benzene (6 ml), triethyl phosphite (0.85 g, 0.005 mole) added and mixture left to react for two hours at room temperature. The reaction mixture was then adsorbed onto a silica column (50 g). Benzene eluted a liquid which crystallised from light petroleum to give 0.2 g (14%) of N,S-diethyl-N'-trichloroacetylthiourea m.p. 37-38° identified by comparison with an authentic sample. Also present in the benzene fraction was a small quantity of 0,0,0,-triethyl thiophosphate.

Further elution with benzene-ether (40:1) gave a compound which crystallised from benzene-light petroleum (1:1) to give 0.33 g (30%) of N'-dichloroacetyl-N-ethylthiourea, m.p. and mixed m.p. 109-111°. Final elution with benzene-ether (20:1) gave a liquid characterised as diethyl phosphorochloridate (0.16 g, 19%) by comparison with an authentic sample.

(b) To obtain an estimate of the yields of the products formed in reaction (a), it was repeated on the same scale and analysed by GLC as for the case of trichloroacetylurea. The four major products all had sufficient stability to pass through the chromatograph. Unfortunately the triethyl phosphate peak was not completely separated from

that of the small amounts of the thiophosphate present. Nevertheless, the detector was calibrated for the other three major components of the reaction mixture. Analysis with n-tridecane as internal standard gave the following results.

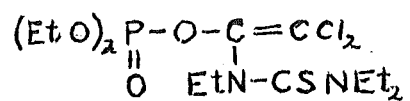
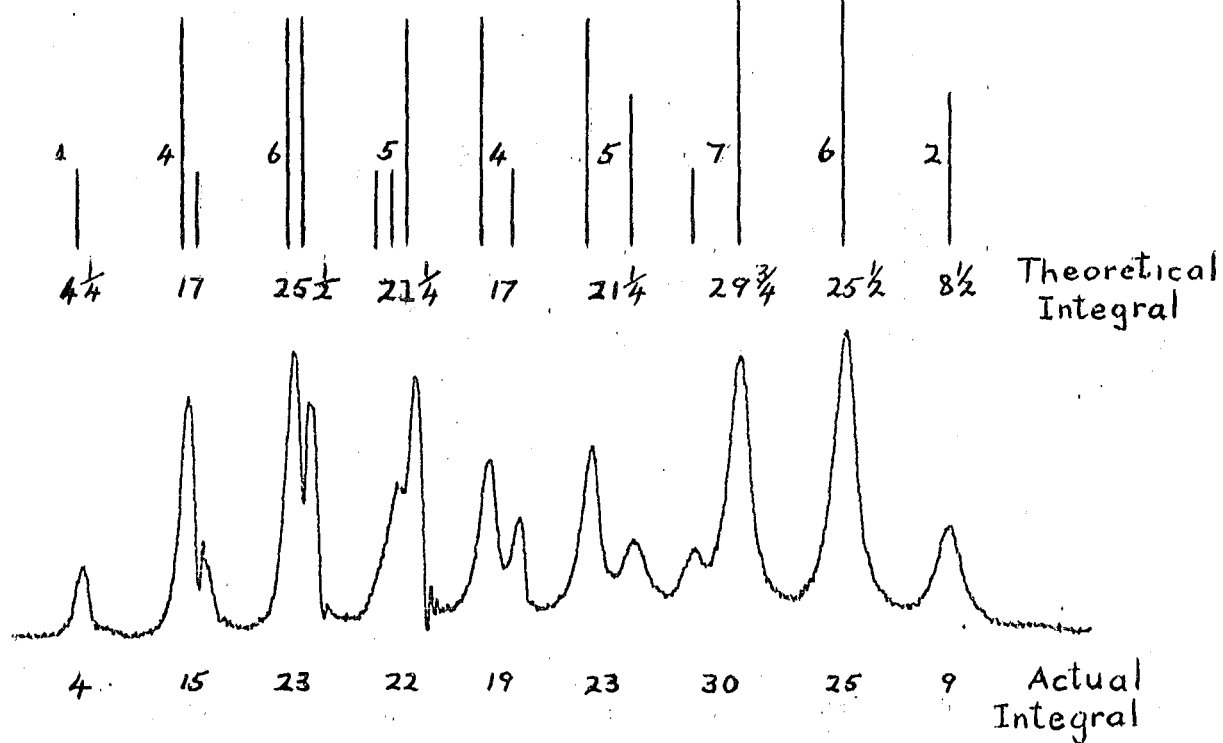
<u>Product</u>	<u>Yield, %</u>
$(\text{EtO})_2\text{P}(\text{O})\text{Cl}$	54
$\text{Cl}_2\text{CHCONHCSNHEt}$	41
$\text{Cl}_3\text{CCON}=\underset{\substack{ \\ \text{SEt}}}{\text{C}}-\text{NHEt}$	22

Analysis of this same reaction by NMR indicated a yield of 44% for the N'-dichloroacetyl-N-ethylthiourea.

Reaction of N-Trichloroacetyl-N,N'-triethylthiourea with Triethyl Phosphite.

N-Trichloroacetyl-N,N',N'-triethylthiourea (1.5 g, 0.005 mole) was dissolved in benzene (3 ml) and triethyl phosphite (1g, 0.0057 mole) added. After heating for six hours at 60°, analysis of a sample by TLC showed that the reaction had given virtually one product. (There were only traces of a compound with R_f value identical to that of the corresponding dichloroacetyl thiourea). The product was isolated by adsorbing the reaction mixture onto a silica column and eluting with benzene-ether (20:1). 1.2 g (64%) of diethyl 2,2-dichloro-1-(N,N',N'-triethylthioureido)vinyl phosphate,

72.

Methylene Protons of $\text{CH}_2-\text{O}-\text{P} \text{ (4 H)}$ $\text{CH}_2-\text{N} \text{ (2 H)}$ $\text{CH}_2-\text{N}' \text{ (4 H)}$ 

(EtO) $\begin{array}{c} \text{P}-\text{O}-\text{C}=\text{CCl} \\ \text{2} \parallel \quad | \quad \text{2} \\ \text{O} \quad \text{NEtCSNet} \end{array}$ was isolated. IR $\sqrt{\text{max}}$ 1635 (C=C),

and 1280 cm^{-1} (P=O). NMR (CCl_4): δ 3.90 (10 protons, multiplet, CH_2) and 1.33 ppm (15 protons, multiplet, CH_3). The multiplet at δ 3.90 ppm can be explained by the overlapping of three different methylene protons 4.18 (P-O- CH_2), 3.90 (N- CH_2) and 3.63 ppm (N'- CH_2). These are drawn up and overlapped to give the complete multiplet (shown opposite).

(Found: C, 38.18; H, 6.19; N, 6.63. $\text{C}_{13}\text{H}_{25}\text{Cl}_2\text{N}_2\text{O}_4\text{PS}$ requires C, 38.33; H, 6.19; N, 6.88%. Mass spectrum, M^+ 406 (0.14%) with significant peaks at m/e (%), 371 (100), 343 (5.5) and 315 (0.79). (M^+ 406.0645. $\text{C}_{13}\text{H}_{25}\text{Cl}_2\text{N}_2\text{O}_4\text{PS}$ requires 406.0650. $\text{M}^+ - \text{Cl}$ 371.0960. $\text{C}_{13}\text{H}_{25}\text{Cl}_2\text{N}_2\text{O}_4\text{PS}$ requires 371.0961).

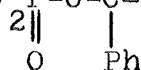
Reaction of Chlorodibenzoylmethane with Triethyl Phosphite.

An investigation of this reaction was carried out using both benzene and acetic acid as solvents.

(a) In benzene

Chlorodibenzoylmethane (0.66 g, 0.0025 mole) was reacted with triethyl phosphite (0.48 g, 0.0029 mole) by refluxing a benzene (4 ml) solution of the two compounds for two hours. Distillation had been reported^{40b} to lead to considerable decomposition, so purification of the reaction product was achieved by adsorption of the reaction mixture on to a silica column (20 g). Elution with

benzene-ether (9:1) gave 0.7 g (79%) of diethyl 2-benzoyl-1-phenylvinyl phosphate, (EtO)₂P-O-C=CHCOPh.



NMR (CCl₄): δ 8.3-7.3 (10 protons, aromatic), 7.15 and 6.92 (1 proton, doublets, J=2 and 1.5 cps resp., C=CH), 4.24 and 4.12 (4 protons, multiplets, J=7 cps, P-O-CH₂) 1.34 and 1.22 ppm (6 protons, triplets, J=7 cps, C-CH₃).

(b) In acetic acid

Chlorodibenzoylmethane (0.33 g, 0.0013 mole) and triethyl phosphite (0.33 g, 0.002 mole) were added to acetic acid (2 ml) and heated at 80° for one hour. After removing most of the acetic acid under reduced pressure, an NMR (CCl₄) spectrum of the reaction mixture showed that there had been an 80% conversion to the enol phosphate. (The olefinic protons δ 7.15 and 6.92 ppm were detected in a ratio of 8:100 relative to the aromatics). The amount of dibenzoylmethane present was insignificant (<10%) as determined from an NMR comparison of the olefinic protons in the enol form of dibenzoylmethane (δ 7.00 ppm) with those of the enol phosphate. An identical reaction in ethanol also gave the enol phosphate as expected. The yield was 84% of theory by NMR.

Reaction of Bromodibenzoylmethane with Triethyl Phosphite.

This reaction has been reported⁴² to give dibenzoylmethane by a free radical mechanism so the reaction was examined under several sets of conditions including those

reported in the literature. Free radical initiators were also used in an attempt to induce the production of dibenzoylmethane.

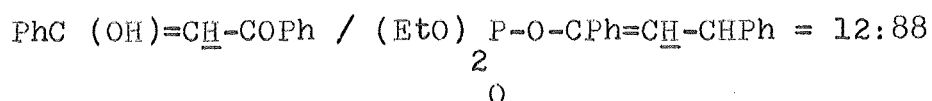
(a) In benzene.

Bromodibenzoylmethane (0.76 g, 0.0025 mole) was dissolved in benzene (4 ml). On adding the triethyl phosphite (0.48 g, 0.0029 mole), an exothermic reaction took place. After it had returned to room temperature, the reaction was left for a further hour before stripping the benzene off under reduced pressure. NMR (CCl_4) showed that there had been 90-100% conversion to enol phosphate (the ratio of olefinic protons to aromatic was 19:200). There was no sign of any dibenzoylmethane in the NMR spectrum ($<5\%$).

The reaction mixture was adsorbed on to a silica column (20 g). Elution with benzene-ether (9:1) gave 0.6 g (65%) of enol phosphate. The IR and NMR spectra were identical with those of the product obtained from the reaction of chlorodibenzoylmethane with triethyl phosphite.

(b) In absence of solvent.⁴²

To 8 g (0.026 mole) of bromodibenzoyl methane was added, dropwise, and with stirring, 4.75 g (0.028 mole) of triethyl phosphite, at such a rate that the temperature of the reaction exceeded 80° . After the addition was complete it was left for an hour. An NMR (CCl_4) analysis on a sample taken from the reaction mixture showed the following proton integral ratios.



and total $\text{C=CH} / \text{aromatic} = 8:100$

indicating a 70% yield of vinyl phosphate and 10% of dibenzoylmethane.

The reaction mixture was distilled at 0.05 mm pressure. The fraction collected 120-180° (5.83 g), had a higher dibenzoylmethane content (38%) than the original reaction mixture indicating distillation was accompanied by some decomposition.

(c) In protic solvents.

(1) Bromodibenzoylmethane (0.76 g, 0.0025 mole) was dissolved in ethanol (4 ml) and triethyl phosphite (0.48 g, 0.0029 mole) added. After one hour, GLC analysis of a sample showed the presence of only two volatile compounds. These had retention times corresponding to those of triethylphosphate and dibenzoylmethane. The solvent was removed from the reaction under reduced pressure and a NMR analysis showed the presence of dibenzoylmethane in 90-100% yield. (The ratio of the olefin proton 7.00 ppm relative to aromatic protons was 19:200).

The reaction mixture was then crystallised from methanol-light petroleum to give 0.4 g (70%) of dibenzoylmethane, which, after recrystallisation from light petroleum had m.p. 78-79°.

(ii) To a mixture of acetylacetone (1 ml) and 1,2-dimethoxyethane (1 ml) was added bromodibenzoylmethane (0.38 g, 0.0013 mole) and triethylphosphite (0.24 g, 0.0015 mole). After one hour, the solvent was stripped off under reduced pressure. NMR (CCl_4) showed the following proton integral ratios.

		<u>Yield.</u>
PhC(OH)=CH-COPh / <u>aromatic</u>	= 17:200	85%
$(\text{EtO})_2\text{P-O-C=CHAc}$ / <u>aromatic</u> <div style="margin-left: 100px;"> $\begin{array}{c} \\ \text{CH}_3 \end{array}$ </div>	= 11:200	56%

These two products were also identified from their GLC retention times. There were no protons in the NMR characteristic of diethyl 2-benzoyl-1-phenylvinyl phosphate. (When this reaction was carried out with benzene/dimethoxyethane as solvent there was still some (ca 5-10%) of the 2-benzoyl-1-phenylvinyl phosphate formed).

(d) In presence of free radical initiators.

Three reactions of bromodibenzoylmethane (0.76 g, 0.0025 mole) with triethyl phosphite (0.48 g, 0.0029 mole) were carried out in the absence of solvent. In one of them, 2,2'-azo-bis-isobutyronitrile (12 mg, 4 mole%) was mixed with the bromodibenzoylmethane before reaction. In the second, 24 mg, (4 mole%) of dibenzoylperoxide was added. The third reaction was used as a control. Neither the first or the second

reactions showed any increase over the 3rd in the amount of dibenzoylmethane detected in the NMR. All were less than 10%. The three reactions were heated at 80° for one hour. Further samples taken for NMR analyses, again failed to show any difference in the amounts of dibenzoylmethane present.

Reaction of Chlorotribenzoylmethane with Triethyl Phosphite.

(a) Reaction in benzene.

Chlorotribenzoylmethane (0.9 g, 0.0025 mole) was added to benzene (4 ml) followed by triethyl phosphite (0.48 g, 0.0029 mole). The mixture was stirred while this was added and for four hours afterwards at room temperature. The mixture was then adsorbed onto a silica column (30 g). Elution with benzene-ether (20:1) gave a gum-like product, diethyl 2,2-dibenzoyl-1-phenylvinylphosphate

(EtO) $\text{P}-\text{O}-\text{C}=\text{C}(\text{COPh})_2$. The yield was 0.87 g (65%).
 $\begin{array}{c} 2\parallel \\ \text{O} \end{array}$ $\begin{array}{c} | \\ \text{Ph} \end{array}$

The IR and NMR were consistent with this structure.

(Found: C, 67.12; H, 5.44; P, 6.87. $\text{C}_{24}\text{H}_{25}\text{O}_6\text{P}$ requires C, 67.24; H, 5.38; P, 6.67%).

(b) Reaction in ethanol.

Chlorotribenzoylmethane (0.45 g, 0.0013 mole) and triethyl phosphite (0.24 g, 0.0015 mole) were added to ethanol (3 ml) and stirred while the temperature of the reaction was raised to 40-50° and held there for one hour. As the chlorotribenzoylmethane slowly dissolved, a fluffy white solid formed until eventually the whole

mixture was nearly solid. After cooling the reaction, this solid was collected by filtration and identified as tribenzoylmethane, m.p. $223-226^{\circ}$ on recrystallisation from acetonitrile. The yield was 0.34 g (83% of theory). This was not depressed when mixed with an authentic sample (m.p. $222-224^{\circ}$).

The filtrate, after removal of the solvent under vacuum, weighed 0.2 g. This was shown to consist of mainly triethyl phosphate (identified by its GLC retention time, and estimated from the NMR as 80-90% pure). The yield of triethyl phosphate was 80-90% of theory.

Control reaction.

A sample of the enol phosphate obtained in reaction (a) was dissolved in ethanol and left standing at room temperature for two days. TLC (acetone-chloroform, 1:20) showed that the enol phosphate was still the only compound present ($R_f = 0.68$). There was no sign of any tribenzoylmethane. When the ethanol was stripped off under vacuum, the residue had an IR identical with that of the starting material.

(c) Reaction in the presence of free radical initiators.

Chlorotribenzoylmethane (0.36 g, 0.001 mole) was mixed with 2,2'-azo-bis-isobutyronitrile (12 mg, 8 mole%) and stirred while triethyl phosphite (0.18 g, 0.0011 mole) was added. A vigorous reaction took place when the reaction was warmed to 40° . It was held there for thirty minutes. An identical reaction was carried out with

dibenzoyl peroxide (12 mg, 5 mole%) as initiator and again a vigorous reaction took place on warming.

TLC showed that the major products of both reactions was the enol phosphate, with no sign of any tribenzoylmethane in either. Yields were of the order of 70% theory (Isolated as in (a)).

A few other compounds which normally gave enol phosphates on reaction with phosphites (see P. 8) were reexamined. In the following three reactions attempts have been made to obtain the dehalogenated product by carrying out the reaction with triethyl phosphite in various protic solvents.

Reaction of 2,2,2-Trichloroacetophenone with Triethyl Phosphite in Acetic Acid.

2,2,2-Trichloroacetophenone (0.56 g, 0.0025 mole) was dissolved in acetic acid (4 ml) and triethyl phosphite (0.48 g, 0.0029 mole) added. After one hour at room temperature the reaction was shown by GLC to contain only one product. This was identified as diethyl 2,2-dichloro-1-phenylvinyl phosphate by a comparison of its retention time with that of an authentic sample. The IR of the reaction mixture, after removal of the acetic acid under vacuum, was identical with that of an authentic sample.

Reaction of 2,2-Dichloroacetophenone with Triethyl Phosphite in Protic Solvents.

2,2-Dichloroacetophenone (0.24 g, 0.0013 mole) and triethyl Phosphite (0.24 g, 0.0015 mole) were

dissolved in the protic solvent (2 ml) and left to react at room temperature for one hour. After removing the solvent under reduced pressure, the reaction was analysed by NMR. The following proton integral ratios were measured.

<u>Reaction solvent</u>	<u>EtOH</u>	<u>CH₃COOH</u>
(EtO) ₂ P(=O)-O-C(=CHCl)- <u>aromatic</u> Ph	18 : 110	22 : 117
<u>Yield of enol phosphate</u>	<u>ca 80%</u>	<u>ca 90%</u>

The enol phosphate in both reactions was also identified by its GLC retention time and shown to be the only major product.

Reaction of Phenyl Trichloroacetate with Triethyl Phosphite in Protic Solvents.

Phenol trichloroacetate (0.3 g, 0.0013 mole) and triethyl phosphite (0.24 g, 0.0015 mole) were dissolved in 2 ml of solvent and heated to 80° for thirty minutes. The solvent was then removed under vacuum and the reaction products analysed by NMR and GLC.

<u>Reaction solvent</u>	<u>Proton integral ratio</u>	<u>Yield %</u>
	Cl ₂ CH- to CH ₃ CN	Cl-CHCO-Ph —2—2—
(a) 0.005M EtOH in benzene	9.5 : 18	<u>ca 50</u>
(b) EtOH	13.5 : 16	<u>ca 85</u>
(c) 0.005M PhOH in benzene	22 : 28	<u>ca 80</u>

GLC showed that along with the triethyl phosphate formed there was still diethyl 2,2-dichloro-1-phenoxyvinyl phosphate in (a) but not in (b). Similarly, there was no enol phosphate detected in (c); only phenyl dichloroacetate and diethyl phenyl phosphate.

Two other solvents, acetic acid, and thiophenol in benzene, also resulted in reduction of the phenyl trichloroacetate to the dichloroacetate without any enol phosphate being detected (GLC).

Phenyl trichloroacetate (5 g, 0.02 mole) was dissolved in benzene (35 ml). Thiophenol (2.4 g, 0.022 mole) and triethyl phosphite (4 g, 0.024 mole) were added. The reaction was then refluxed for thirty minutes before the solvent was distilled off under vacuum. The residue was distilled through a 10 cm column at 0.5 mm pressure. The fraction collected at 70-80° (3 g, 70%) was recrystallised from hexane to give 1.3 g (30%) of phenyl dichloroacetate, m.p. and mixed m.p. 46-48°.

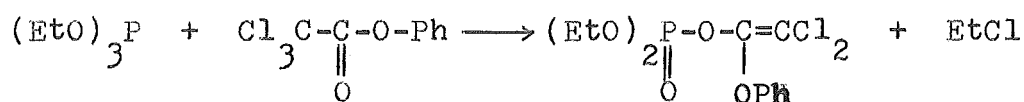
A further fraction collected at 110-120° had an IR and GLC retention time identical with that of O,O-diethyl S-phenyl phosphorothiolate. The yield was 2.9 g (60%). (Lit. b.p. 182-186°/30mm).

Kinetic Studies

An examination of the kinetics of enol phosphate formation or dehalogenation have so far not been reported in the literature. Since a knowledge of the order of these

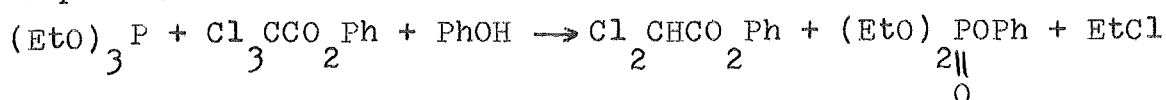
reactions could lead to a greater understanding of the mechanism, the variation of the rates of reaction with initial concentration of triethyl phosphite, α -halogeno-carbonyl compound and proton source was determined.

The system chosen for study was the reaction of phenyl trichloroacetate with triethyl phosphite in benzene with and without phenol. In the absence of phenol, dehalogenation did not occur, the sole product of the reaction being the enol phosphate.



That this reaction was, as expected, first-order in both triethyl phosphite and phenyl trichloroacetate was confirmed by measurements of initial rates (first 10% of reaction) of enol phosphate formation at 50° for varying concentrations of reactants. The rate of reaction was followed by measuring the rate of appearance of the enol phosphate using GLC. Reliable rate constants for this reaction could not be obtained because difficulty was met in getting reproducible values for the enol phosphate concentration using the flame ionization detector. The results obtained, however, were considered accurate enough for the reaction order to be determined.

If sufficient phenol were present in the system no enol phosphate was formed. Instead the products of the reaction were now phenyl dichloroacetate and diethyl phenyl phosphate.



The course of this reaction could be followed by GLC determination of both the rate of formation of phenyl dichloroacetate, and, (as a check) the rate of disappearance of phenyl trichloroacetate. n-Tridecane was used as an internal standard and the detector was calibrated using a standard mixture of the three compounds*. The results obtained were :

<u>Rate of Formation of Phenyl Dichloroacetate</u> <u>at 25° in Benzene/Phenol</u>			
$[(\text{EtO})_3\text{P}]$	$[\text{Cl}_3\text{CCO}_2\text{Ph}]$	$[\text{PhOH}]$	$\frac{\text{Initial Rate} \times 10^3}{(\text{moles.l}^{-1}.\text{min}^{-1})}$
0.1	0.1	0.15	4
0.2	0.1	0.15	8.8
0.1	0.05	0.15	2.2
0.1	0.1	0.45	12.9

These results indicate that under the conditions investigated the rate of dehalogenation is first-order not only in triethyl phosphite and phenyl trichloroacetate, but also first-order in phenol. The mean value for the third-order rate constant, $k=2.85 \text{ l}^2.\text{mole}^{-2}.\text{min}^{-1}$ is considered to be reliable to $\pm 15\%$.

* The concentrations of these were comparable with those encountered in the reactions. On column injection, with a 2.5' column of 3.5% APL on Chromosorb P was used for the analysis. The column had an initial temperature of 85° and a programme of 2°/minute was used.

Table I

REACTION OF $\text{Cl}_3\text{C-CO-NH-CO-Y}$ WITH $(\text{EtO})_3\text{P}$ (EQUIMOLAR)

85.

Reaction Conditions				Product Yields, %			
<u>Reaction No.</u>	<u>Y</u>	<u>Solvent</u>	<u>$[\text{Cl}_3\text{CCONHCOY}]$</u>	<u>$(\text{EtO})_3\text{PO}$</u>	<u>$\text{Cl}_2\text{CHCONHCOY}$</u>	<u>$(\text{EtO})_2\text{P}-\underset{\text{O}}{\underset{\text{NHCoy}}{\text{C}}}=\text{CCl}_2$</u>	<u>Others</u>
1	NH_2	benzene	1.3 M	30-40	41 ^b	—	$(\text{EtO})_2\text{P(O)Cl}$ trace
2		PhOH 1.1M in benzene	0.56 M	20-40	85 ^b	—	$(\text{EtO})_2\text{P(O)OPh}$ 45
3	NMe_2	benzene	(2.4 M)	32 ^a	22 ^b , 37 ^d	8 ^c	—
4		benzene	0.7 M	40 ^c	35 ^d	16 ^d	—
5	CH_2Cl	benzene	0.46 M	46 ^a	45 ^a	20 ^c	—

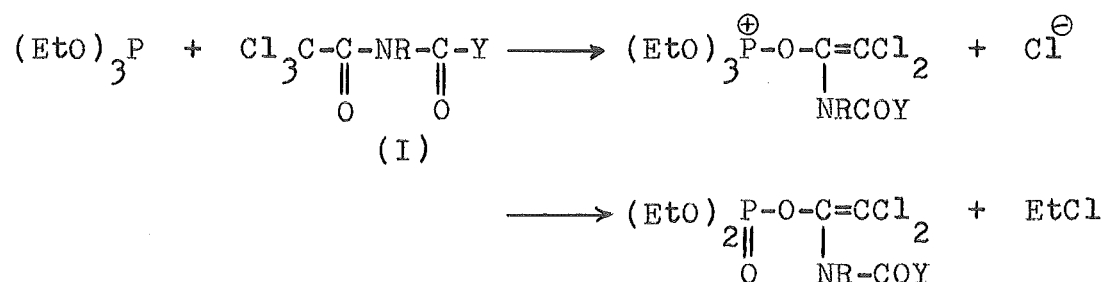
^aIsolated by distillation. ^bCrystallised from reaction. ^cIsolated by column chromatography. ^dCrystallised from reaction + column chromatography of residue.

RESULTS AND DISCUSSION

In the introduction it was mentioned that trichloroacetamides react with phosphites to give vinylamine derivatives,¹⁵ e.g.

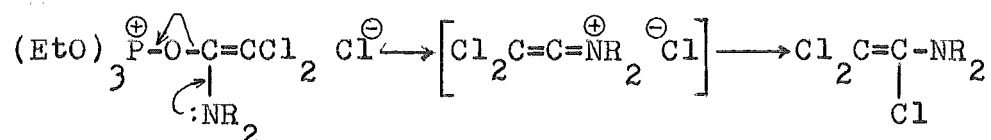


If one of the R groups attached to the nitrogen atom is replaced by an electron-withdrawing carbonyl or sulphonyl group the normal Perkow reaction occurs,³⁹



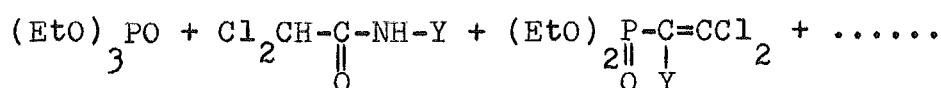
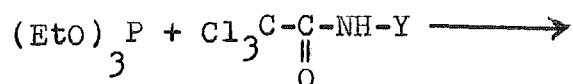
Y = H, R', COR' or CO₂R'

suggesting that it is the availability of the lone pair of electrons on the nitrogen which leads to formation of the keteniminium salt and hence the vinylamine.



In this work the reactions of (I), where R = H, have been investigated. The initial results of the reactions studied are summarised in Table I. The major products obtained in these reactions were the corresponding dichloroacetamide derivatives and triethyl phosphate. Although the yields of these were all less than 50%, the

only other products that could be identified were vinyl phosphonates and the yields of these were low.



(II)

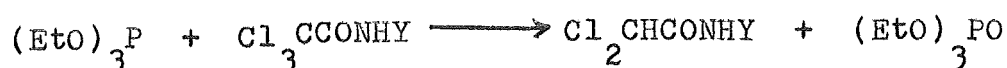
The dehalogenated products, (II), could conceivably arise in a number of ways and these will be considered in turn. The formation of vinyl phosphonate is also unexpected and will be discussed separately.

Possible Origins of Dehalogenated Products

An examination of the product yields in Table I shows that in all cases much of the halogenocarbonyl compound undergoes dehalogenation. The yields of vinyl phosphonates are sufficiently low for the formation of these compounds to be considered (at the present stage of the discussion, at any rate) to be a competing side reaction. It is also apparent that even in the most favourable cases there are considerable amounts of unidentifiable by-products. In fact, on the average, isolated compounds account for only about 50% of the crude reaction product. For this reason conclusions based entirely on yields may be unreliable.

A consideration of the phosphorus balance in reaction 5 (Table I) leads to the conclusion that the dehalogenation

process is accompanied by the formation of at least some triethyl phosphate, and in most reactions the amounts of phosphate are sufficiently great to suggest an overall stoichiometry of

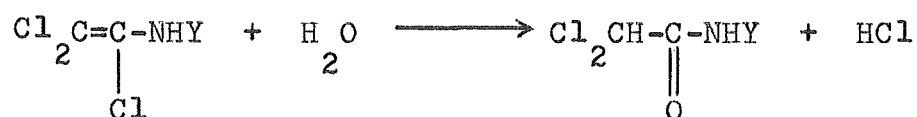


in the main reaction. In order to obtain the necessary products from the starting materials, however, it is necessary to add the elements of water to the left-hand side.



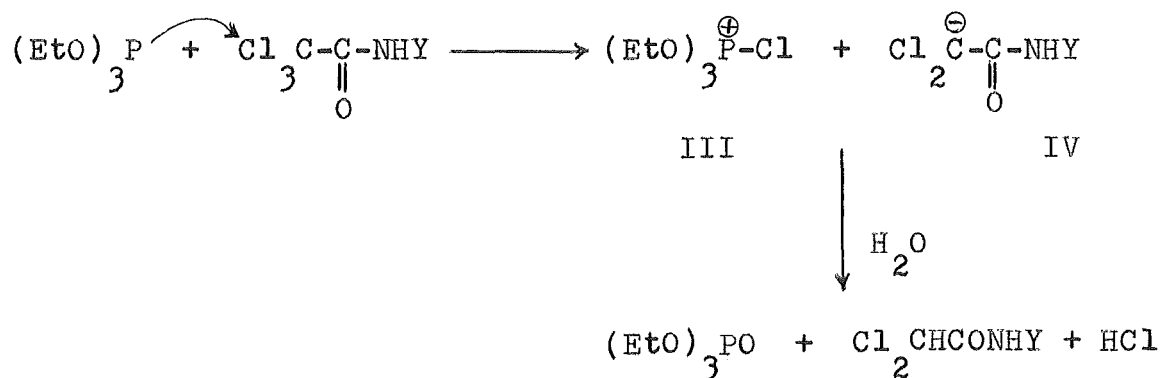
If traces of water were present in the reaction mixture it could lead to the formation of the required products by either of two mechanisms:

(a) Hydrolysis of intermediates such as vinylamines.



These compounds are products of the reaction of certain trichloroacetamides (see p.23) and are known to react with water.¹⁵

(b) By hydrolysis of the products of phosphite attack on halogen, if such attack did occur.

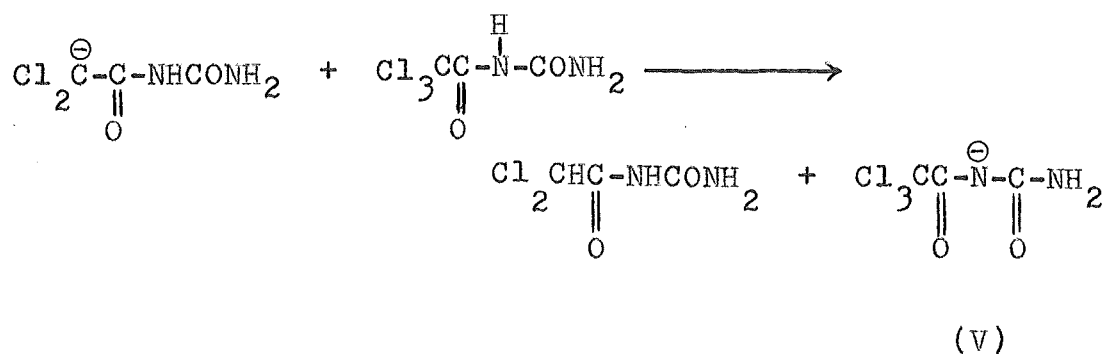
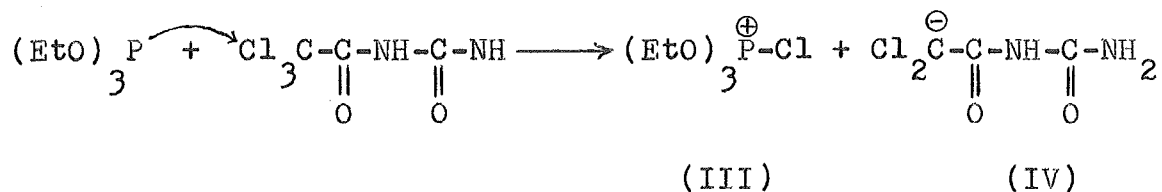


Scheme 1

However, all attempts to exclude moisture from the reaction of trichloroacetylurea with triethyl phosphite failed to prevent dichloroacetylurea from crystallising out from the reaction mixture. Although this ruled out hydrolysis by paths (a) and (b), it is still possible that some attack at halogen was occurring because of the small amounts of diethyl phosphorochloridate detected in the reaction (reaction 1, Table 1). This phosphorochloridate probably results from dealkylation of the intermediate chlorophosphonium cation (III) (see example p.5).

An alternative explanation for the formation of the dehalogenated product also involves initial attack by phosphite on halogen but does not require the intervention of water. In this case the product forms as a result of the transfer of a proton to the dichloroacetyl anion(IV) from a second molecule of starting material. Such a

mechanism also accounts satisfactorily for the low yields obtained in these reactions.



Scheme 2

The only drawback to this scheme is that no previous case has been reported of the trapping of the anion produced from attack by phosphite on an α -halogenocarbonyl compound

Evidence for an Ionic Mechanism of Dehalogenation

The small amounts of phosphorochloridate detected in the reaction of trichloroacetylurea could have resulted from the dealkylation of the phosphonium cation III by either of the ureide anions (IV) or (V), but these would be more likely to attack positive phosphorus than they would saturated carbon.

Table II

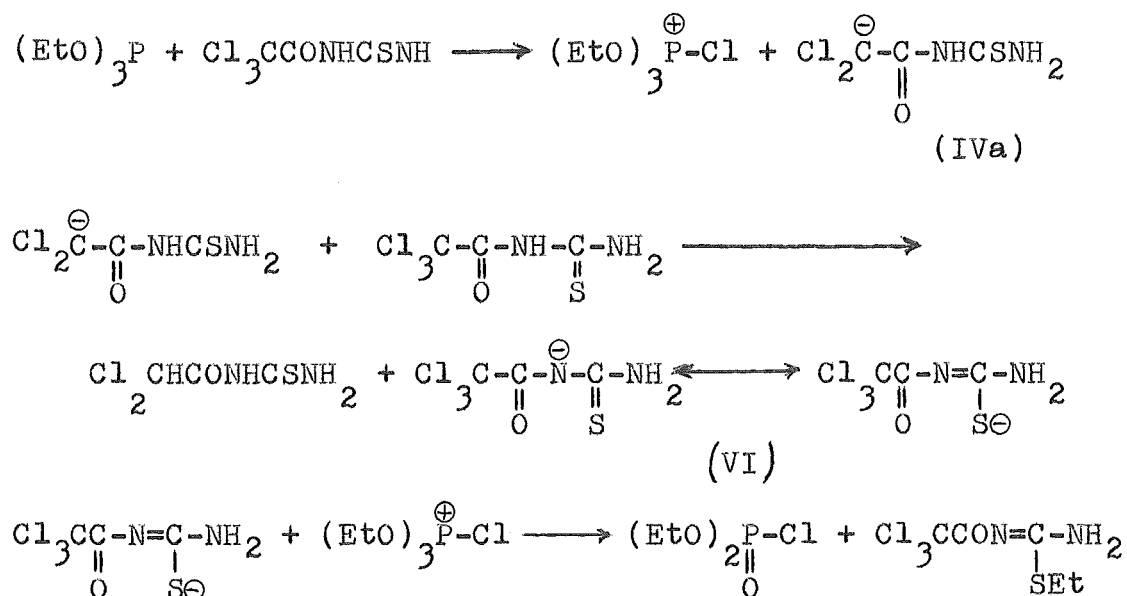
REACTION OF $\text{Cl}_3\text{C-CO-NH-CS-Y}$ WITH $(\text{EtO})_3\text{P}$ (EQUIMOLAR)

91.

Reaction Conditions			Product Yields, %				
<u>X</u>	<u>Y</u>	<u>$[\text{Cl}_3\text{CCONHCSY}]$</u>	<u>$(\text{EtO})_2\text{P(O)Cl}$</u>	<u>$(\text{EtO})_3\text{PO}$</u>	<u>$\text{Cl}_2\text{CHCONHCSY}$</u>	<u>$\text{Cl}_3\text{CCON}=\underset{\text{SEt}}{\text{C}}-\text{Y}$</u>	<u>Enol</u> <u>Phosphate</u>
H	NH ₂	0.7 M in benzene	56 ^e	15 ^e	66 ^f , 18 ^b	32 ^f , 6 ^b	—
		0.56 M in ethanol	—	80-100 ^g	85 ^f	—	—
H	NHEt	0.74 M in benzene	54 ^e	some ^e	44 ^e , 41 ^f , 30 ^c	22 ^e , 15 ^c	—
Et	NEt ₂	benzene	—	—	—	—	64 ^c

^bCrystallised from reaction. ^cIsolated by column chromatography. ^eGLC analysis.^fNMR analysis. ^gOnly product detected by GLC.

Isothioureide anions, on the other hand, are more likely to act preferentially as dealkylating agents because of the high nucleophilicity of sulphur towards saturated carbon. Table II lists the results obtained when trichloroacetylthioureas were used instead of trichloroacetylureas. Both N-trichloroacetylthiourea and N-ethyl-N'-trichloroacetylthiourea, on reaction with triethyl phosphite, gave, in addition to the expected dichloroacetyl compounds, good yields of diethyl-phosphorochloridate and the S-ethyl trichloroacetyl-isothiourea. The S-alkylated starting material is unreactive toward triethyl phosphite and consequently at the end of the reaction an appreciable amount of the latter remains unconsumed. The overall reaction is therefore best represented by the following reaction scheme.



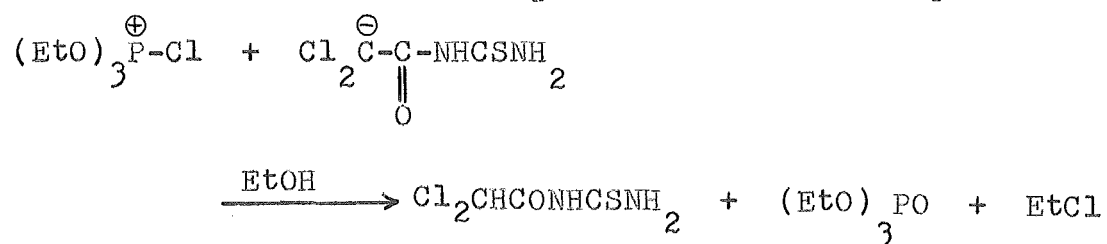
Scheme 3

There was no evidence for the presence of $\text{Cl}_2\text{CH}-\text{CO}-\text{N}=\underset{\begin{array}{c} | \\ \text{SEt} \end{array}}{\text{C}}-\text{NH}_2$

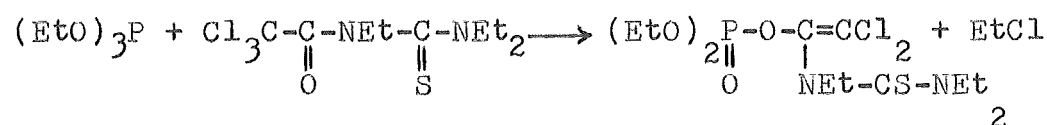
in the product, so it is likely that the dichloroacetyl anion (IVa) once formed abstracts a proton from a second molecule of starting material to form the dehalogenated product. The resulting trichloroacetylisothioureido anion (VI) acts as the dealkylating agent.

The small amounts of triethyl phosphate detected in the reaction may arise from the action of traces of water on the ions produced in the first step of the reaction.

Further evidence for the Scheme 3 outlined is provided by the observation that increased yields of the dichloroacetylthiourea are obtained by carrying out the reaction in protic solvents, e.g. ethanol (Table II). The anion (IV) can now abstract a proton from the solvent in preference to one from a second molecule of trichloroacetylthiourea because of the large excess of ethanol present

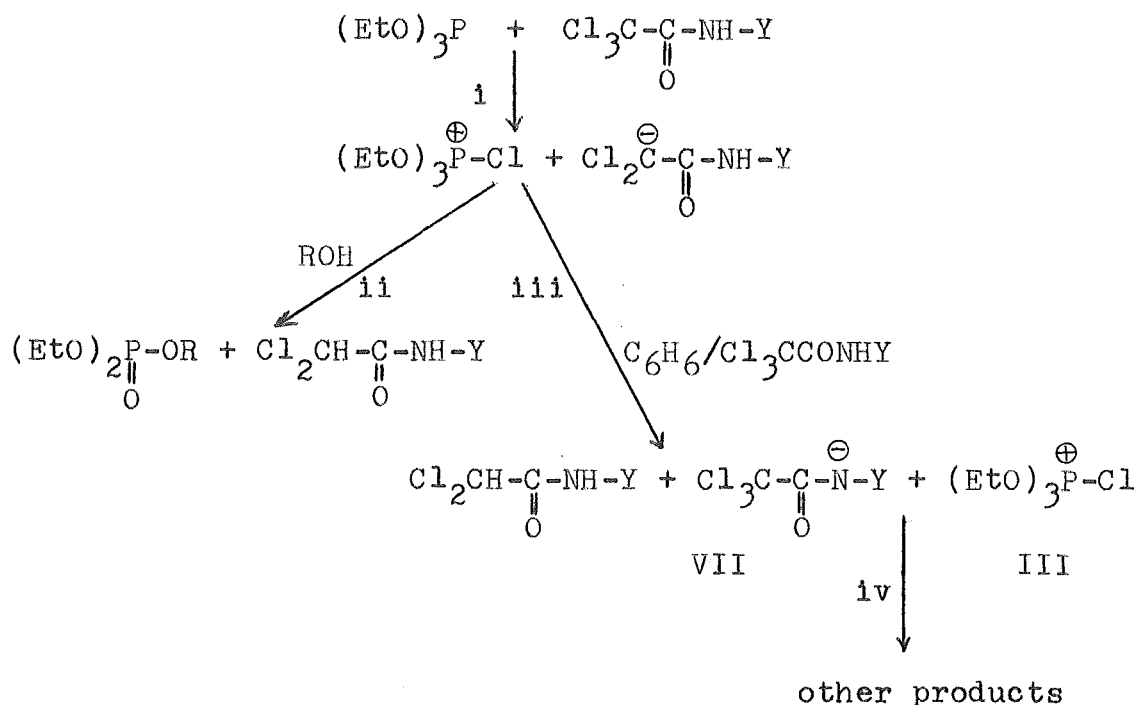


The only product isolated from the comparable reaction of N-trichloroacetyl - N,N',N'-triethylthiourea with triethyl phosphite was the enol phosphate, diethyl 2,2-dichloro-1-(N,N',N'-triethylthioureido)vinyl phosphate



The anion formed in attack by phosphorus at halogen can not now be trapped since there is no acidic proton in the starting material and the normal product of the Perkow reaction is obtained.

Fully substituted ureas and amides of the type $\text{Cl}_3\text{CCONRCOY}$ similarly give enol phosphates on reaction with triethyl phosphite,³⁹ so it is likely that the other reactions summarised in Table I also occur by initial attack at halogen followed by protonation of the anion by a second molecule of starting material. This was again substantiated by the increase in yield of dichloroacetylurea observed when the reaction of trichloroacetylurea with triethyl phosphite was carried out in benzene containing excess phenol. Thus the reaction appears to be a general one.

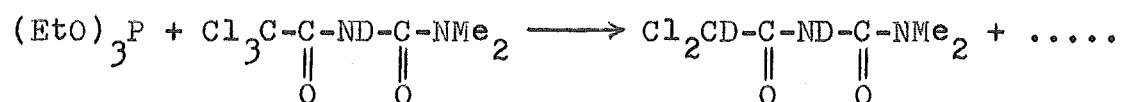


Y = electron-withdrawing group

Scheme 4

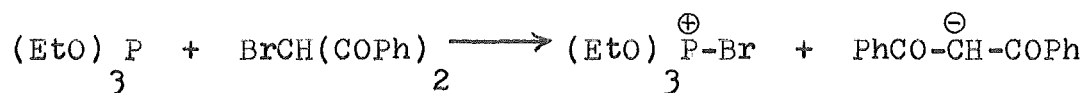
However only in the case where Y is a thioamide group were products that resulted from the final stage iv of this scheme, isolated (Scheme 3 P. 92). In the reaction where Y is an amide group, triethyl phosphate was the major phosphorus product isolated. This could arise in a number of ways, including the interaction of the chlorophosphonium cation III with the imidoyl anion (VII) (path iv, Scheme 4). This part of the reactions was not investigated further because the main point of interest was in the initial step (1) where compounds, which were very similar to those that gave enol phosphates on reaction with trialkyl phosphites, appeared to be reacting by initial attack on halogen by phosphorus.

Finally, as further evidence of the ionic, as opposed to free radical nature of these reactions, the reaction of N-deutero-N',N'-dimethyl-N-trichloroacetyl-urea with triethyl phosphite was studied. The dichloro-acetylated urea obtained as product had a deuterium atom on the α -carbon.



This is consistent with the ionic mechanism shown in Scheme 4, but not one involving a free radical, which is more likely to abstract an α -hydrogen atom, e.g. $\text{CH}_2\text{-O}$, $\text{CH}_3\text{-N}$, than the most acidic proton.⁶⁵

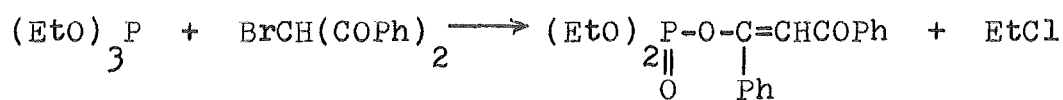
initial attack on halogen along with interference from moisture or some other protic species.



Scheme 5

In view of this alternative interpretation it was considered necessary to repeat their work on triethyl phosphite and attempt to show that an enolate anion resulting from attack on halogen was formed. This was considered to be easier than to try and show that radicals did or did not participate in the dehalogenation reactions observed in their work.

When the reaction of bromodibenzoylmethane with triethyl phosphite was carried out on a small scale, it was found that, contrary to Arbusov's results, the major product was the enol phosphate. This was the case both when benzene was used as a solvent and in the absence of solvent.



All efforts to induce formation of dibenzoylmethane as the major product by the addition of free radical initiators failed, so other possible reasons for the formation of reduction products observed by Arbusov were investigated.

As small amounts (< 10%) of dibenzoylmethane were found when the above reactions were carried out in the absence of solvent, it was possible that they resulted from disproportionation of the enol phosphate due to heat generated by the exothermic nature of the reaction (This enol phosphate is known to disproportionate at ca 150°).^{40b} To check this, the reaction was conducted on the same scale and under the same conditions employed by Arbusov, making sure at the same time that the temperature rose above the 80° reportedly reached by their reaction. Analysis of the crude product by NMR showed that the enol phosphate had still formed in good yields along with approximately 10% of dibenzoylmethane. Hence it is not likely that the dibenzoylmethane (61%) which Arbusov reported resulted from disproportionation. Since the radical mechanism appeared at this point very improbable, the proposal that dehalogenation occurred as a result of attack of phosphite on halogen followed by reaction of the anion with protic species present was investigated (see Scheme 5 P.97). Such a mechanism had been suggested earlier in a review by Harvey and De Sombre.⁴⁴ If this pathway were correct then it would be the first case noted where the use of protic solvents changed the course of

a reaction from enol phosphate to dehalogenation.

Reactions in ethanol and acetylacetone, again with bromodibenzoylmethane (Table III. P.102), gave good yields (80-90%) of dibenzoylmethane. These reactions show that the dibenzoylmethane obtained by Arbusov could well have resulted from the enolate anion being trapped by protic species if they were present in the reaction.

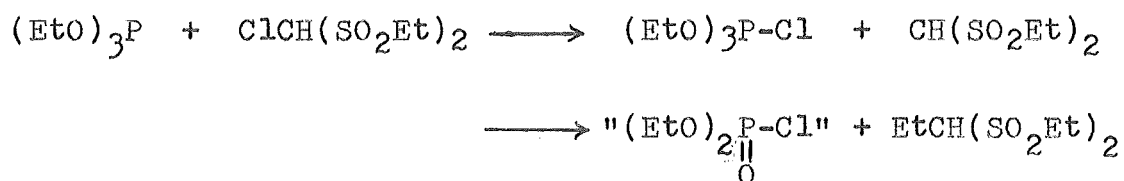
Kreutzkamp and Kayers⁴¹ also observed reduction of chloro- derivatives of β -dicarbonyl compounds (chlorobenzoylacetone and chlorotribenzoylmethane) on reaction with triethyl phosphite. They too suggested a radical mechanism on the basis that it was accelerated by UV radiation and peroxides. However, since this time, chlorobenzoylacetone has been shown by Pudovik and Biktimirova to give the enol phosphate^{40b} in 60-80% yield.



The work of Kreutzkamp and Kayser on chlorotribenzoylmethane has been repeated in benzene solvent and has been shown (Table III P.102) to give enol phosphate and not dehalogenated product. Tribenzoylmethane could not be obtained from this reaction even with free radical initiators present, but a good yield (83%) was isolated when the reaction was carried out in ethanol as solvent. Experimental details for this work of Kreutzkamp and Kayser were not reported so it was not possible

to repeat their work under identical conditions or to know how real the acceleration of the reactions under UV radiation was (it is possible that the acceleration claimed may have been a result of heat, for in the course of this work it was noticed that although reaction was slow at room temperature in the absence of solvent, when it was warmed to 30-40° a vigorous exothermic reaction followed).

The last three compounds mentioned on P.26 are halogen derivatives of disulphones. Their reactions with triethyl phosphite were also studied by Arbusov and Bogonostseva and were claimed to involve the participation of free radicals.⁴³ The major products obtained were the reduction products of the starting disulphones and triethyl phosphate as well as some ethylation products of the disulphones. The formation of these last two products could not be explained by the authors. In the light of recent work it seems that the ethylated disulphonated resulted from alkylation by the chlorophosphonium cation produced by initial attack on halogen.



The triethyl phosphate formation might result from an intermediate, similar to that involved in the Perkow reaction,

Table III

REACTION OF $\text{R}-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{Y}$ WITH $(\text{EtO})_3\text{P}$ (EQUIMOLAR)

Reaction conditions			Product Yields, %		
<u>R</u>	<u>Y</u>	<u>Solvent</u>	<u>Dehalogenated</u>	<u>Enol Phosphate</u>	<u>$(\text{EtO})_2\text{P}(\text{O})\text{OR}'$</u>
CCl_3	NMeCONHMe	Ac_2CH_2 2.2M in glyme	75 ^f	25 ^f	65 ^f
CHClCOPh	Ph	benzene	—	78 ^c	—
		acetic acid	—	80 ^f	—
		ethanol	—	84 ^f	—
CHBrCOPh	Ph	benzene	—	90 ^f	—
		no solvent	10 ^f	70 ^f	—
		ethanol	90 ^f , 70 ^b	—	80-100 ^g
		Ac_2CH_2 2.2M in glyme	85 ^f	—	60 ^f
$\text{CCl}(\text{COPh})_2$	Ph	benzene	—	65 ^c	—
		ethanol	83 ^b	—	80-100 ^g
CCl_3	Ph	acetic acid	—	80-100 ^g	—
CHCl_2	Ph	acetic acid	—	90 ^{f,g}	—
CCl_3	OPh	ethanol	85 ^f	—	80-100 ^g

^bCrystallised from reaction. ^cIsolated by column chromatography. ^fNMR analysis.

^gOnly product detected by GLC.

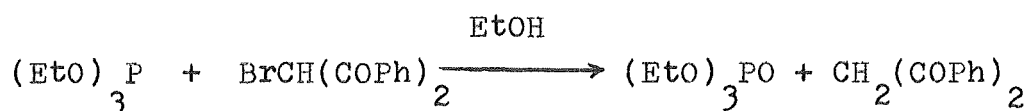
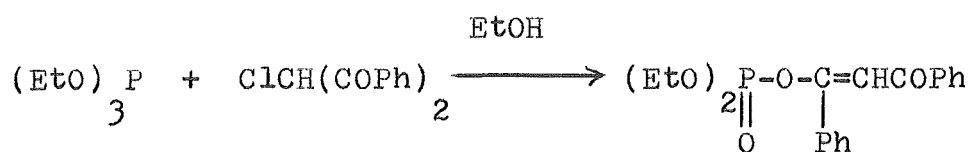
phosphite under aprotic conditions, some of these were attempted in protic solvents. The results of these are summarized in Table III.

The first reaction investigated was that of N,N'-dimethyl-N-trichloroacetylurea, chosen because of its similarity of structure to those compounds in Table I (P. 85). When the reaction was carried out using 2.24 M acetylacetone in glyme (1,2-dimethoxyethane) as a solvent, a considerable amount (75% of theory) of the corresponding dichloroacetylated urea was formed. The enol phosphate was still formed to the extent of 25% but its formation could probably have been completely suppressed by increasing the concentration of acetylacetone.

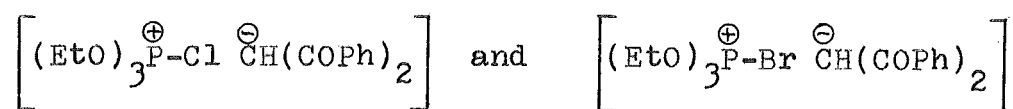
Chlorodibenzoylmethane still gave good yields of enol phosphate even with acetic acid as solvent, as did 2,2-dichloro- and 2,2,2-trichloroacetophenone. In the series of ketones;

ClCH_2COPh , Cl_2CHCOPh , Cl_3CCOPh , $\text{ClCH}(\text{COPh})_2$, $\text{ClC}(\text{COPh})_3$; it is not until there are three carbonyl groups present α to the chlorine atom that attack on the chlorine atom predominates over attack on the carbonyl group. In the case of the corresponding bromo-derivatives attack at halogen occurs more easily and dehalogenation is observed in the case of bromodibenzoylmethane.

The reaction of phenyl trichloroacetate was investigated in various protolytic solvents (Table III) and was found to give the dichloroacetate quite readily.



The intermediates for these reactions would be



respectively. The second of these would be the more reactive because of the better leaving ability of the bromide ion, yet this is the intermediate which gives dibenzoylmethane as products in protic solvents.

Hence, for those reactions giving enol phosphates in protic solvents, it can be said that attack at halogen does not occur, or if it does, is very slow by comparison with the rate of enol phosphate formation.

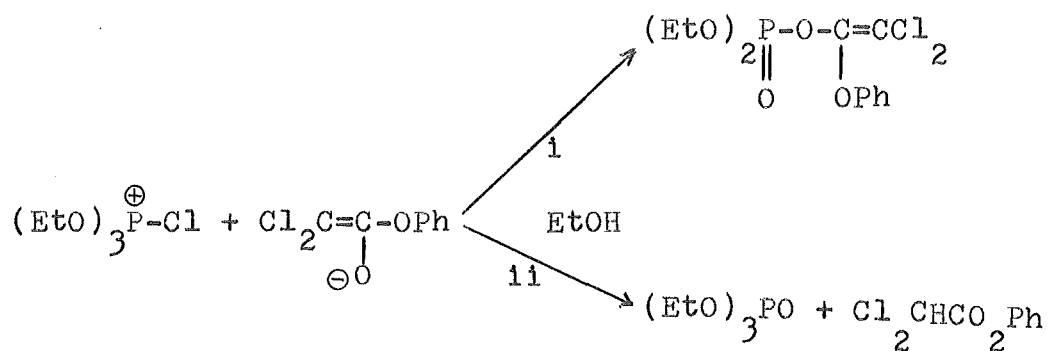
The reactions of phenyl trichloroacetate in various solvents showed two important trends: 1. Increasing the concentration of the proton source increases the yield of dichloroacetate relative to that of enol phosphate, and 2. Increasing the acid strength of the proton source increases the relative yield of dichloroacetate.

Table IV

REACTION OF $\text{Cl}_3\text{CCO}_2\text{Ph}$ WITH $(\text{EtO})_3\text{P}$			
Solvent	$[\text{ROH}]/[\text{Cl}_3\text{CCO}_2\text{Ph}]$	Products (% yield)	
		$\text{Cl}_2\text{CHCO}_2\text{Ph}$	$(\text{EtO})_2\text{P}-\text{O}-\text{C}(=\text{O})\text{CCl}_2$ $\begin{array}{c} \text{O} \quad \text{OPh} \\ \parallel \quad \end{array}$
$\text{EtOH}/\text{C}_6\text{H}_6$	4	50 ^a	some ^c
EtOH	28	85 ^a	0 ^c
$\text{PhOH}/\text{C}_6\text{H}_6$	4	80 ^a	0 ^c
$\text{PhSH}/\text{C}_6\text{H}_6$	1.1	70 ^b	0 ^c

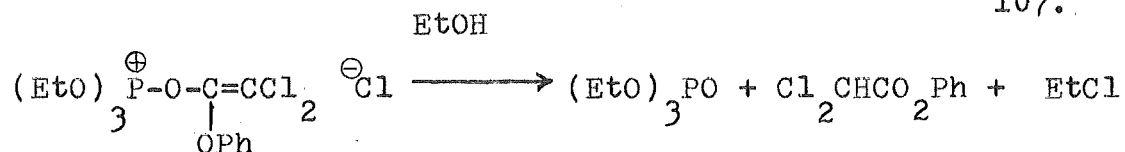
^a Yield determined by NMR ^b Isolated ^c GLC

These effects are those expected for the following two competing reactions.

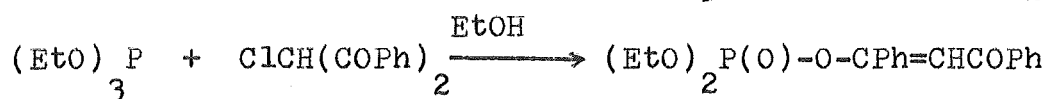
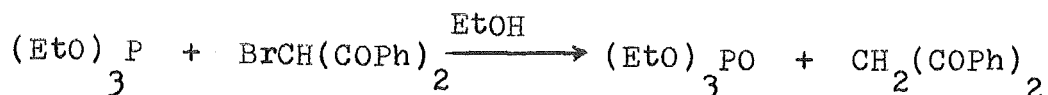


Regardless of whether these are the slow steps of the overall reaction or whether the formation of the ions is rate determining, an increase in ethanol concentration will favour path (11) at the expense of path (1).

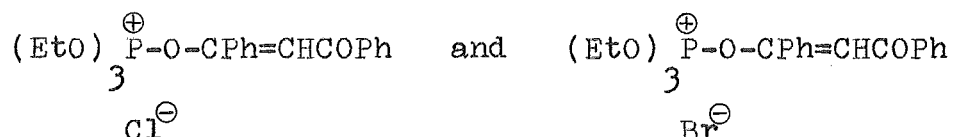
It is not likely that the observed products arose from solvolysis of the enol phosphonium intermediate, i.e.



as different products were obtained from the reactions of chloro- and bromodibenzoylmethanes in ethanol.



The two enol phosphonium intermediates of these reactions are similar



yet the products would require that the latter only be attacked by ethanol and then lose alkyl halide. This is clearly unreasonable so it appears that the final irreversible dealkylation is too fast for solvolysis to occur.

The enol phosphates were shown to be stable under the conditions of the reactions. This effectively ruled out the possibility of dehalogenation occurring through their solvolysis :



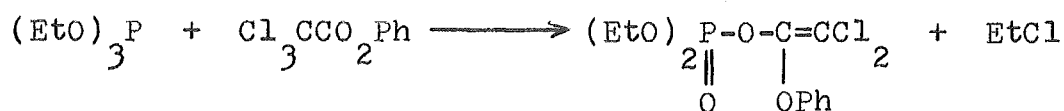
A simple kinetic investigation of this reaction of phenyl trichloroacetate with triethyl phosphite in

benzene containing phenol revealed that the reaction giving the dichloroacetate was first-order in all three reagents.



third-order reaction

In the absence of phenol the reaction giving enol phosphate was first-order in triethyl phosphite and in trichloroacetate.



second-order reaction

(A discussion of the mechanistic aspects of this situation will be given later, see P.117)

The Formation of Vinyl Phosphonates.

The major benefit gained from this kinetic study was from the practical aspect in relation to the first group of reactions investigated (Table I P.85). The effect of the acidic imide proton should be reduced, provided the proton exchange involved was an inter- and not an intramolecular transfer, by carrying out the reactions in dilute solutions.

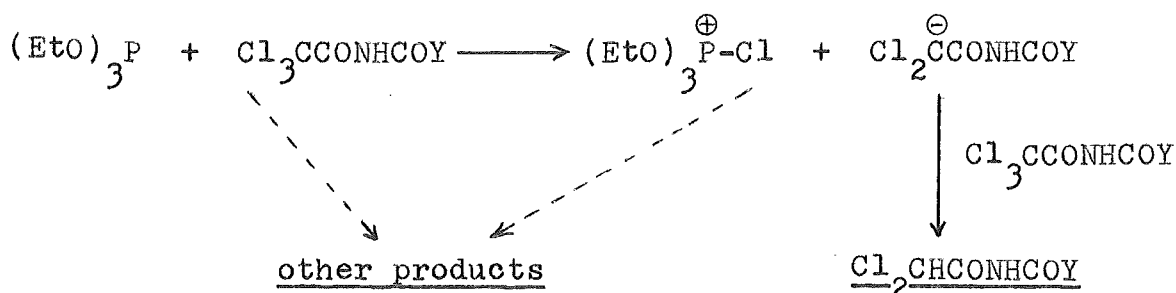


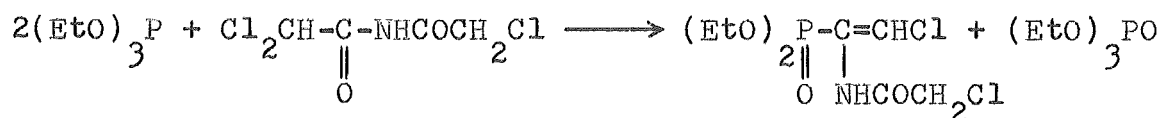
Table V
REACTION OF X-CCl₂-CO-Y WITH (EtO)₃P

Reaction conditions					Product Yields, %		
No.	X	Y	[XCCl ₂ COY]	$\frac{[(\text{EtO})_3\text{P}]}{[\text{XCCl}_2\text{COY}]}$	(EtO) ₃ PO	(EtO) ₂ $\overset{\text{P}}{\underset{\text{O}}{\parallel}}\text{-C}=\underset{\text{Y}}{\text{C}}\text{XC1}$	(EtO) ₂ $\overset{\text{P}}{\underset{\text{O}}{\parallel}}\text{-O-C}=\underset{\text{Y}}{\text{C}}\text{XC1}$
1	Cl	NHCONH ₂	0.07 M	2	85 ^a	48 ^c	—
2	Cl	NHCONMe ₂	0.08 M	2	83 ^a	50 ^b	—
3	Cl	NHCOCH ₂ Cl	0.1 M	2	84 ^a	35 ^b	—
4	H	NHCOCH ₂ Cl	No Solvent	2	75 ^a	38 ^b , 44 ^d	—
5	H	NHCO ₂ Et	No Solvent	2	72 ^a	40 ^c	—
6	H	NCH ₃ COCH ₃	No Solvent	1	—	—	78 ^a
7			PhOH/2 mole	1	—	—	45 ^f
8	H	NCH ₃ CO ₂ Et	No Solvent	1	—	—	77 ^a

^aIsolated by distillation. ^bCrystallised from reaction. ^cIsolated by column chromatography. ^dCrystallised from reaction + column chromatography of residue. ^fNMR analysis.

Vinyl phosphonates had already been isolated as minor products from two of these reactions, so an attempt was made to increase their relative yield by diluting the reaction 10 fold. However one additional factor was involved.

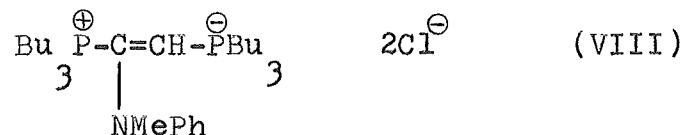
Preliminary experiments carried out on the reaction between triethyl phosphite and N-chloroacetyl-dichloro-acetamide (chosen because this compound is not dehalogenated by phosphite) indicated that the formation of one mole of vinyl phosphonate consumed two moles of triethyl phosphite, the extra phosphite turning up at the end of the reaction as triethyl phosphate.



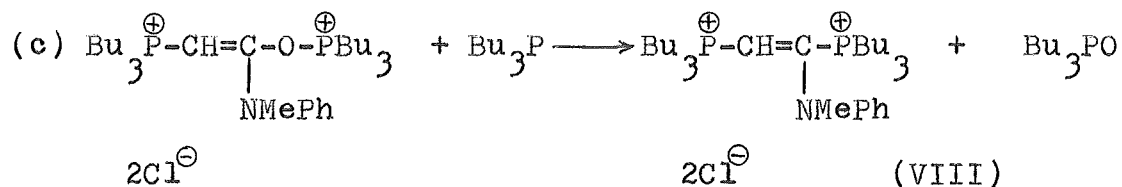
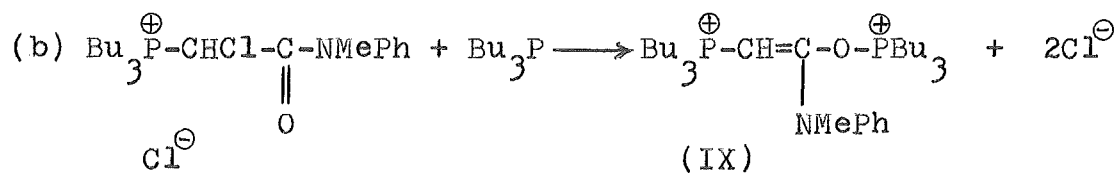
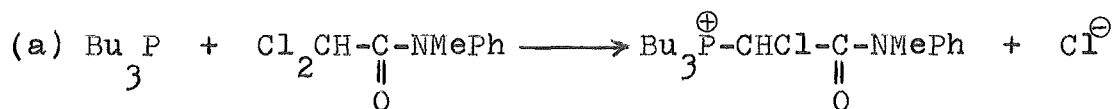
When some of the trichloroacetamide derivatives, that had earlier been observed to undergo dehalogenation when reacted with one equivalent of triethyl phosphite (Table I P.85), were reacted in dilute solution with two equivalents of phosphite, good yields of vinyl phosphonates and triethyl phosphate were obtained (Table V). The yields of dehalogenated products obtained under these conditions were negligible.

Although vinyl phosphonates are known compounds,⁶⁶ there have been no reports in the literature of the formation of ones of the type prepared in this work. An

analogous compound,



had been prepared by Speziale and Smith by the reaction of N-methyl-2,2-dichloroacetanilide with three moles of tri-n-butylphosphine.²¹ They accounted for its formation by suggesting the mechanism below.

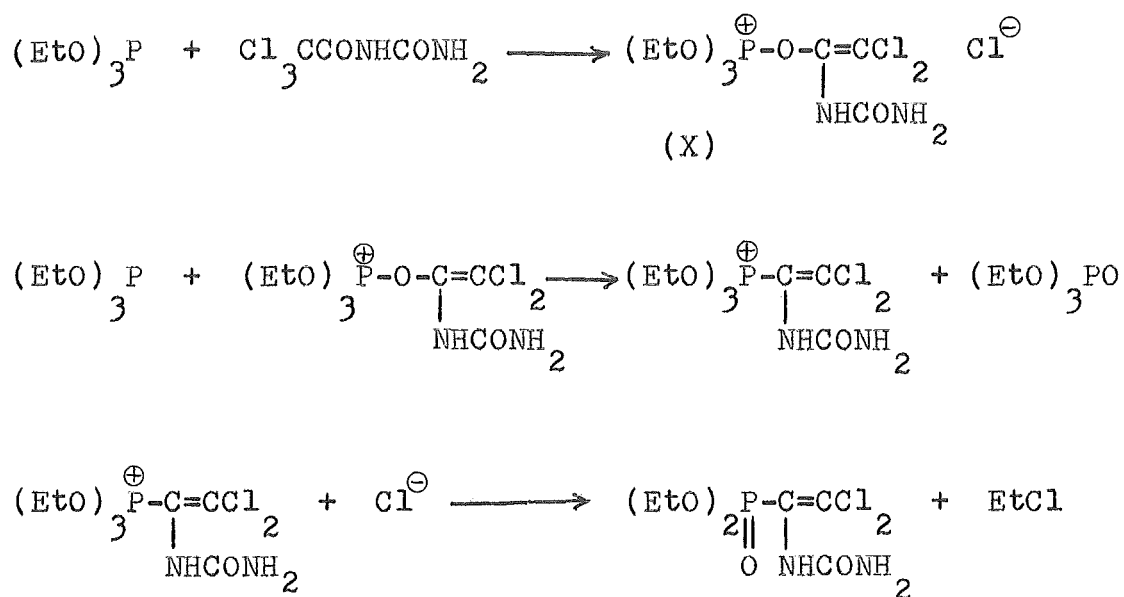


Scheme 6

The first stage, (a), is a simple quaternisation of one molecule of the phosphine by reaction with an alkyl halide. The second, (b), is the formation of an enol phosphonium salt and from a mechanistic point of view can be considered as equivalent to the first stage of a Perkow reaction.

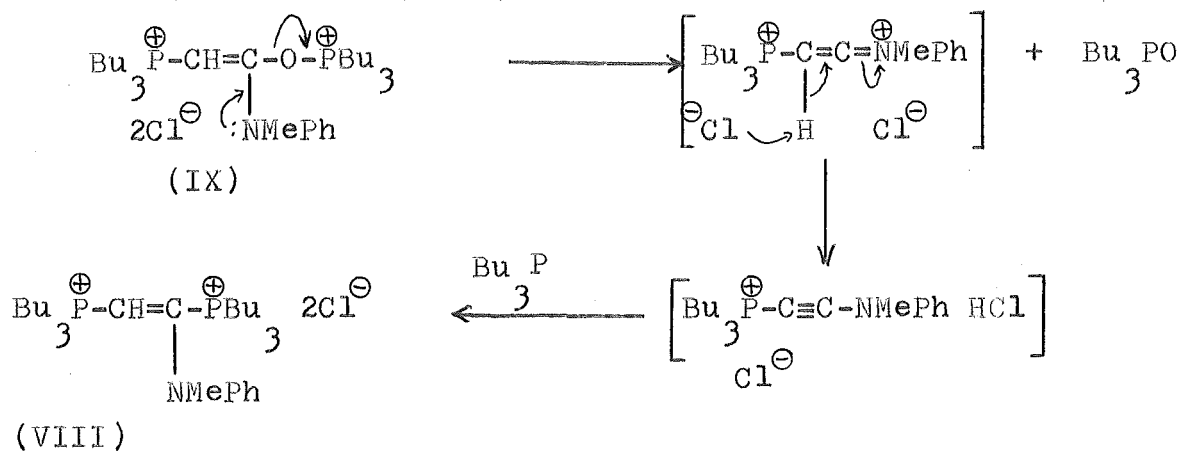
Finally, in the third stage, (c), the enol phosphonium salt (IX) is attacked by a third molecule of tributylphosphine, a molecule of tributylphosphine oxide being displaced. In step (c) they suggest that attack by the phosphine occurs in preference to attack by chloride ion, which would normally give the chlorovinylamine, because of the lack of carbanion stabilization on the α -carbon and hence displacement requires the more nucleophilic tributylphosphine.

An adaptation of this mechanism to the reactions investigated in this work would lead to the following scheme for trichloroacetylurea:



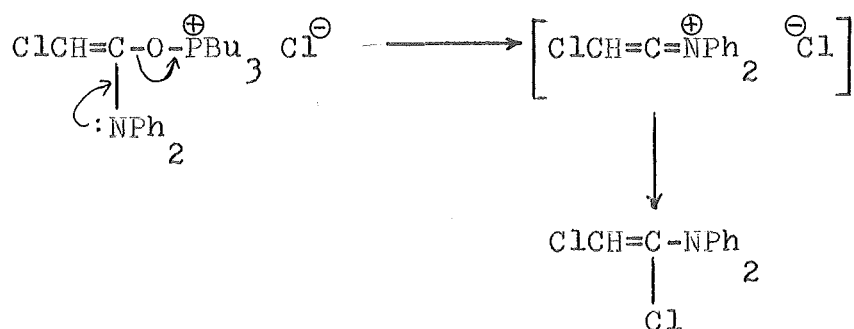
Scheme 7.

enamine (VIII) from (IX) (Scheme 6 P. 111), i.e.

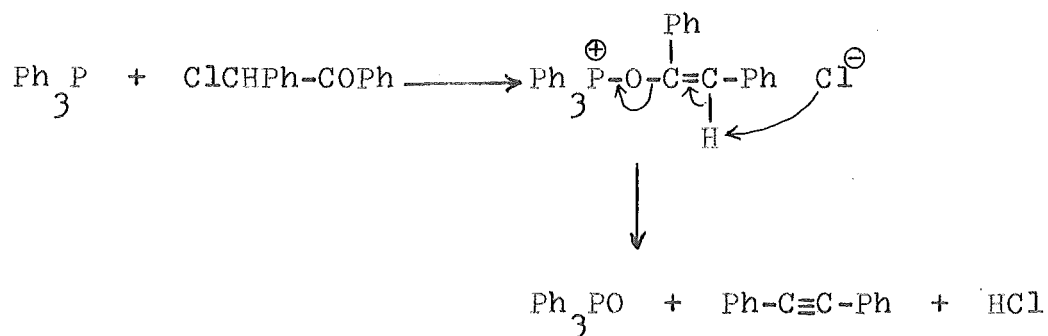


Scheme 9

whereas other intermediates give chlorovinylamines. e.g.



Both of the Schemes 8 and 9 show a resemblance to the mechanism proposed⁷¹ to account for the formation of diphenylacetylene from the reaction of α -phenylphenacyl chloride with triphenylphosphine.⁶⁷



Reactions of Dichloroacetamide Derivatives

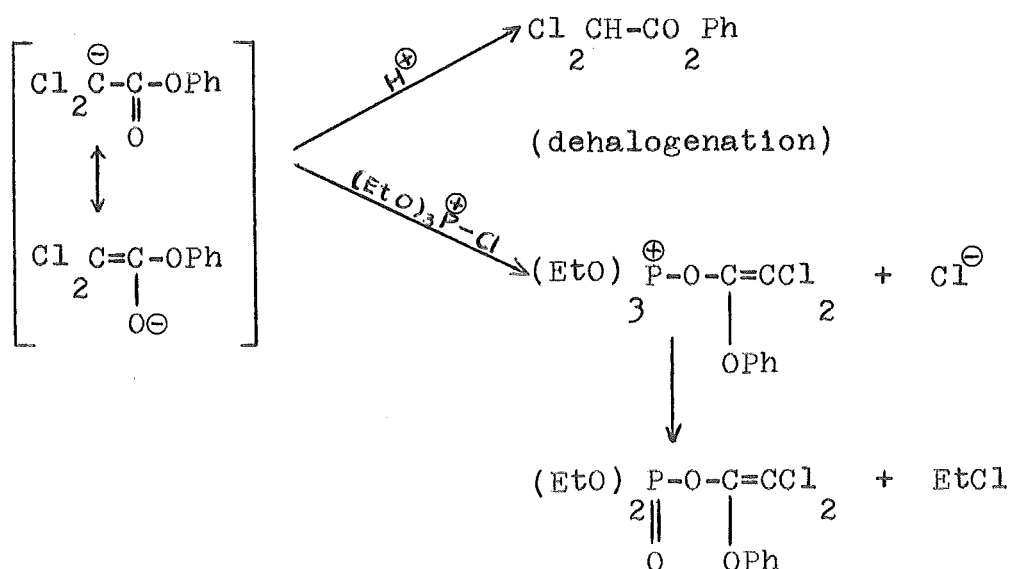
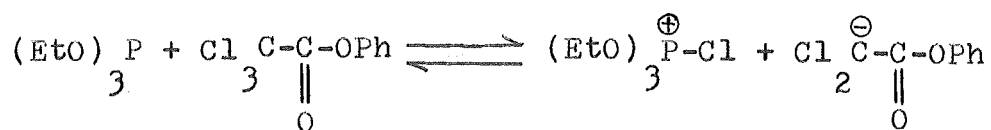
There have been few reports on the reactions of esters and amides of dichloroacetic acid with trialkyl phosphites. The esters do not appear to give isolatable products¹³ while only certain amides²¹ react even with triphenylphosphine. In contrast to this it was found during the course of this work that dichloroacetyl derivatives of the type $\text{Cl}_2\text{CHCONRCOY}$ ($\text{R} = \text{H}, \text{CH}_3$ and $\text{Y} = \text{OEt}, \text{CH}_3, \text{CH}_2\text{Cl}$) reacted quite readily with triethyl phosphite to give either vinyl phosphonates ($\text{R} = \text{H}$) or enol phosphates ($\text{R} = \text{CH}_3$, Table V P.109). Since it has been assumed that an enol phosphonium intermediate is formed in each case, and that this is formed in some way by the nucleophilic attack of triethyl phosphite on the carbonyl group, then the greater reactivity observed for these compounds can be attributed to the strong -T effect of the -COY group.

For the case of N-acetyl-N-methyldichloroacetamide, an enol phosphate was obtained even in the presence of phenol, indicating that, for this compound at least, and probably also for the other dichloroacetyl compounds, attack of phosphite on halogen is not important. This explains why vinyl phosphonates can be obtained from dichloroacetyl derivatives even in the absence of a solvent, while for the case of the corresponding trichloroacetyl compounds, considerable dilution with an inert

solvent is necessary.

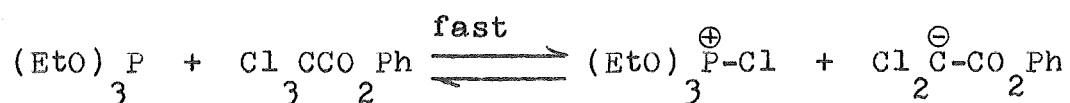
Mechanism of the Perkow Reaction.

So far very little has been mentioned about the significance of the results obtained with respect to the mechanism of the Perkow reaction. It has been suggested however, that the dehalogenation reactions observed in the presence of protic species have occurred by protonation of the enolate anion produced by attack at halogen. Hence for these reactions, attack at halogen as a possible mechanism for the Perkow reaction can now no longer be ruled out so easily (P.18), as the results provide clear evidence that the enolate anion and, presumably, the chlorophosphonium cation exist under the conditions of the Perkow reaction. If the dichloroacetyl anion and chlorophosphonium cation are intermediates involved in the formation of the enol phosphate, a possible overall scheme would be the one below (for phenyl trichloroacetate).

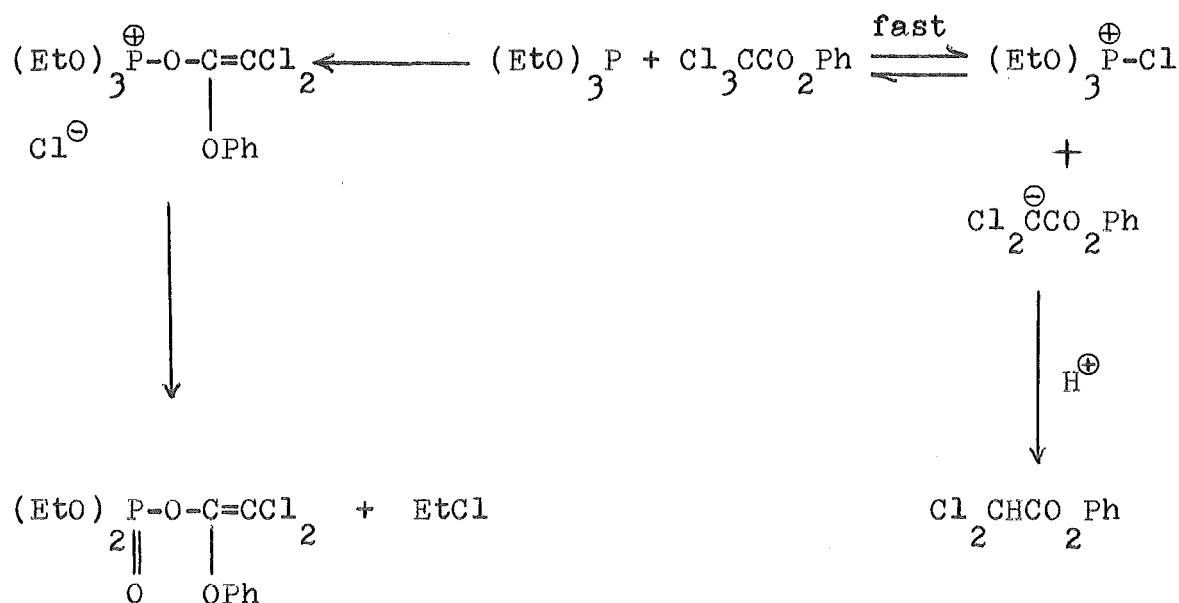


Scheme 10

In order to account for the observations that (1) the formation of both enol phosphate and dehalogenated product is first-order in both triethyl phosphite and phenyl trichloroacetate and (2) the formation of dehalogenated product is first-order in phenol (if present), it is necessary to postulate that attack on halogen is not rate determining, but is a fast equilibrium reaction.



Unfortunately none of the results obtained require that the chlorophosphonium cation and dichloroacetyl anion be intermediates in enol phosphate formation - only in the dehalogenation reaction. The observations are also consistent with the scheme below.

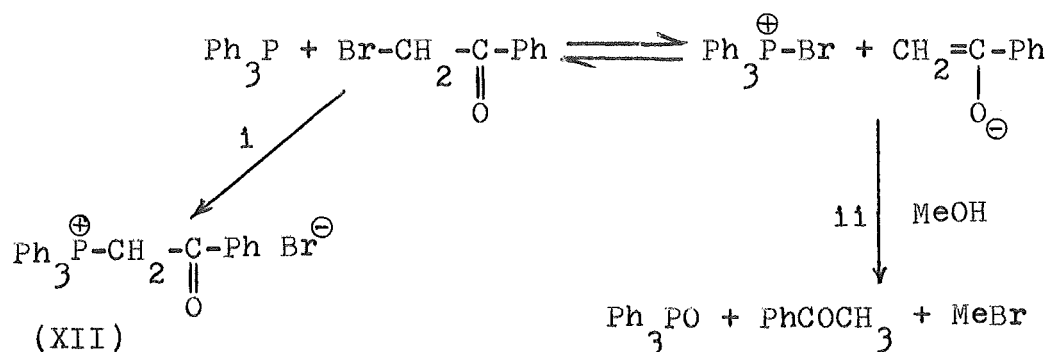


Scheme 11

That is, if the assumption is made that halogen attack is reversible, and this appears to be necessary in order to explain the kinetic data, it is not necessary that the attack at halogen do anything other than compete with enol phosphate formation.

An alternative explanation of the products and the first-order dependence of the rate of dehalogenation on alcohol concentration invokes a concerted reaction involving prior or concurrent protonation of the incipient enolate anion by the protic species present.

protic species, other products being formed by attack elsewhere, e.g. α -carbon in reaction (1) (Scheme 13)



Scheme 13

Evidence for this is provided by the work of Borowitz and Parnes⁷⁰ who have shown that the formation of the C-phosphonium salt (XII) occurs by direct $\text{S}_{\text{N}}2$ displacement of bromide since the reaction is only weakly accelerated ($\rho = +0.44$) by electron-withdrawing substituents on the phenyl group yet the reaction in methanol gives the dehalogenated acetophenone.

It seems therefore that the results obtained for the reaction of phenyl trichloroacetate with triethyl phosphite can be best explained by Scheme 11 (P.119). Scheme 10 (P.118) can not be excluded, but in the absence of good evidence supporting halogen attack as the mechanism of enol phosphate formation, and in view of the evidence against it in other cases (see Introduction P.16) it seems probable the Perkow reaction proceeds by initial attack on the carbonyl group.

CONCLUSION

Whilst it has been shown that for some α -halogeno-carbonyl compounds, reaction with triethyl phosphite in protic solvents occurs by a mechanism involving phosphorus attack on halogen, it has not been possible to show conclusively that such an attack occurs as the initial step of the Perkow reaction. However this possibility can no longer be ruled out except for those cases where the enol phosphate formation is unaffected by protic solvents.

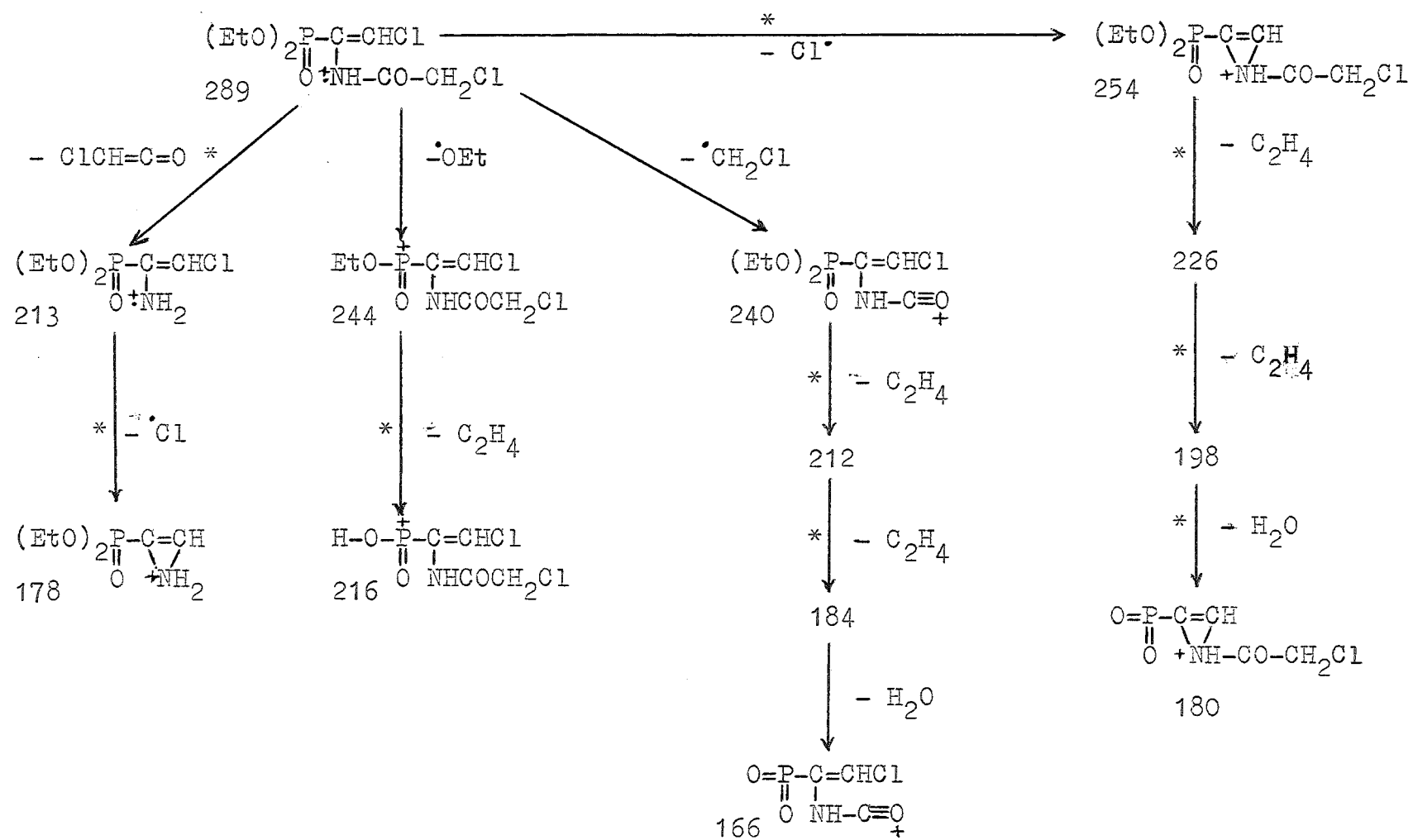
Other dehalogenation reactions reported in the literature could not be reproduced except in the presence of protic solvents. In the absence of any evidence to substantiate the claims of the authors for free radical participation, it seems likely that these reactions also result from initial attack by phosphorus on halogen along with interference from extraneous moisture or other protic species present.

In cases where the α -halogenocarbonyl compound also contains an acidic hydrogen, interference from this can be minimised by conducting the reaction in dilute solution.

As a result of this work attack at halogen has now been established as a feasible mechanism for the Perkow

reaction, especially for trichloroacetic acid derivatives. It does not appear through, that the mechanism can ever be fully elucidated just from a study of reaction products. A more detailed kinetic study would need to be undertaken. Even then, one cannot envisage one mechanism along accounting for the great range of carbonyl compounds which have been observed to take part in the Perkow reaction.

Suggested Fragmentation Paths for $(\text{EtO})_2\text{P}(\text{C}=\text{CHCl})\text{NHCOCH}_2\text{Cl}$



APPENDIX

Identification of the Vinyl Phosphonates

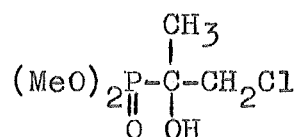
The products from the reactions of trichloro- and dichloroacetamide derivatives (listed in Table V p.109) with a two molar ratio of triethyl phosphite, were assigned vinyl phosphonate structures, i.e. $(\text{EtO})_2\text{P}-\text{C}=\text{CXCl}$, on the basis of a mass spectrum as well as the results of elemental analyses and IR and NMR spectra.

The mass spectrum (see p. 64) obtained for the compound from the reaction 4 (Table V) can be interpreted by the scheme shown opposite. For fragmentations labelled * appropriate metastable peaks were present in the spectrum. The large number of significant peaks in the high m/e region is in marked contrast to the few obtained in the spectrum (p. 66) of the enol phosphate $(\text{EtO})_2\text{P}-\text{O}-\text{C}=\text{CHCl}$. This behaviour is consistent with a phosphonate structure.

The IR spectra showed absorption at $1570 - 1580 \text{ cm}^{-1}$ for the 2,2-dichlorovinyl phosphonates and at 1600 cm^{-1} for the 2-chlorovinyl phosphonates. This can be attributed to the presence of a carbon-carbon double bond and is in agreement with the absorption at 1600 cm^{-1} found by Speziale and Smith²¹ for the analogous compound (VIII) (see p.111).

This region of absorption is quite distinct from that of an enol phosphate usually found in the region 1670 - 1630 cm^{-1} . The spectra also contained peaks characteristic of secondary amide absorption e.g. 3250, 1650 and 1520 cm^{-1} .

The NMR spectra all contained a broad peak in the region δ 6.2 - 8.3 ppm characteristic of an amide proton. This peak in most cases was split into a doublet with a coupling constant $J_{PH} = 0-6$ cps. This is similar to $J_{PH} = 4$ cps found for the O-H proton in the -hydroxyphosphonate¹⁷



The olefin proton of the vinyl phosphonates

$$\text{(EtO)}_2\underset{\begin{array}{c} \parallel \\ \text{O NH-COY} \end{array}}{\text{P}}-\text{C}=\text{CHCl}$$

was also a doublet $J_{PH} = 8$ cps. This coupling constant is considerably larger than that found in enol phosphates $(EtO)_2P(=O)-O-C(=CHCl)NMeCOY$, ($J_{PH} = 0-3$ cps) where the proton is

further removed from the phosphorus atom.

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